Characterizing white matter microstructure of the reward system in depression

This thesis is submitted for the degree of Doctor of Philosophy at Cardiff University

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Thesis summary

This thesis demonstrates the relationship between depression symptomatology and white matter microstructure.

Chapter 1 provides a systematic literature overview on white matter microstructure alterations of the reward system in depression. Findings suggest that localization and extent of white matter microstructure alterations in depression is highly dependent on the state (depression vs. remission) and the clinical subtype.

Using a novel tractography algorithm, Chapter 2 provides a comprehensive instruction on how to delineate the two different branches of the MFB (supero-lateral medial forebrain bundle (slMFB) and infero-medial medial forebrain bundle (imMFB)), the main pathway of the reward system. An association between fractional anisotropy (FA), a diffusion tensor imaging (DTI)-based measure that is supposed to reflect white matter microstructure and hedonic tone, the capacity to derive pleasure from rewarding experiences is identified across a group of remitted depressed (RD) and never depressed (ND) young women.

Chapter 3 uses a longitudinal design to investigate white matter microstructural changes of different pathways of the reward system from depression to remission. A distinct pattern of changes that depends on both the tract and the age is identified.

Chapter 4 investigates the structural correlates of physical activity (PA). PA is reduced in depression and its benefit for depression symptomatology is well known. Using an MRI-sequence that has been shown to be specific to myelination we identify a positive correlation between PA and myelination of the right parahippocampal cingulum (PHC).

This thesis contributes to the identification of structure-function associations related to the reward system in both patients with major depressive disorder (MDD) and healthy controls (HC). Results call for a careful stratification of clinically meaningful homogeneous subgroups if investigating participants with depression. Further the benefit of novel imaging methods for reconstruction of specific pathways and for a neurobiologically meaningful interpretation of the data is clearly shown.

Publications resulting from work in this thesis

Bracht, T., Linden, D.E., Keedwell, P.A., accepted. A review of white matter microstructure alterations of pathways of the reward circuit in depression. Journal of affective disorders.

Bracht, T., Doidge, A.N., Keedwell, P.A., Jones, D.K., 2015. Hedonic tone is associated with left supero-lateral medial forebrain bundle microstructure. Psychological medicine 45, 865-874.

Bracht, T., Jones, D.K., Muller, T.J., Wiest, R., Walther, S., 2015. Limbic white matter microstructure plasticity reflects recovery from depression. Journal of affective disorders 170, 143-149.

Bracht, T., Jones, D.K., Bells, S., Walther, S., Drakesmith, M, Linden, DE., accepted. Myelination of the right parahippocampal cingulum is associated with physical activity in young healthy adults. Brain Structure and Function.

Additional related publications to which I have contributed

Bracht, T., Horn, H., Strik, W., Federspiel, A., Schnell, S., Höfle, O., Stegmayer, K., Wiest, R., Dierks, T., Müller, T.J., Walther, S., 2014. White matter microstructure alterations of the medial forebrain bundle in melancholic depression. Journal of affective disorders 155, 186-193.

Bracht, T., Horn, H., Strik, W., Federspiel, A., Razavi, N., Stegmayer, K., Wiest, R., Dierks, T., Müller, T.J., Walther, S., 2014. White matter pathway organization of the reward system is related to positive and negative symptoms in schizophrenia. Schizophrenia research 153, 136-142.

Declaration

This work has not been submitted in substance for any other degree or award at this or any other university or place of learning, nor is being submitted concurrently in candidature for any degree or other award.

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This thesis is the result of my own independent work/investigation, except where otherwise stated.
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Glossary of abbreviations

ACC	Anterior cingulate cortex
AD	Axial diffusivity
ADC	Apparent diffusion coefficient
AL	Activity levels
ALIC	Anterior limb of the internal capsule
ATR	Anterior thalamic radiation
BADDS	Bipolar Affective Disorder Dimension Scale
BDI	Beck-Depression-Inventory
BDNF	Brain derived neurotrophic factor
CB	Cingulum bundle
CHARMED	Composite hindered and restricted model of diffusion
dACC	Dorsal anterior cingulate cortex
DBS	Deep brain stimulation
dlPFC	Dorsolateral prefrontal cortex
dRL	Damped Richardson Lucy algorithm
DSM IV	Diagnostic and statistical manual of mental disorders
DTI	Diffusion tensor imaging
DWI	Diffusion weighted imaging
FA	Fractional anisotropy
FCPS	Fawcett Clark Pleasure Scale
fMRI	Functional MRI
fODF	Fibre orientation density function
FSPGR	Fast spoiled gradient recalled sequence
HC	Healthy controls
HR	Healthy relatives
imMFB	Infero-medial medial forebrain bundle
IQ	Intelligence quotient
McDESPOT	Multicomponent driven equilibrium pulse observation of T1 and T2
MFB	Medial forebrain bundle
MD	Mean diffusivity
MDD	Major depressive disorder
MINI	Mini International Neuropsychiatric Inventory
MCP	Middle cerebellar peduncle
MRI	Magnetic resonance imaging
NAcc	Nucleus accumbens
NART	National adult reading test
ND	Never depressed
OFC	Orbitofrontal cortex
PA	Physical activity
PET	Positron emission tomography
PD	Parkinson's Disease
PHC	Parahippocampal cingulum
RaD	Radial diffusivity

RD	Remitted depressed
ROI	Region of interest
slMFB	Supero-lateral medial forebrain bundle
SNP	Single nucleotide polymorphism
TE	Echo time
TBSS	Tract based spatial statistics
TR	Repetition time
UF	Uncinate Fasciculus
VBA	Voxel based analyses
VBM	Voxel based morphometry
VMPFC	Ventromedial prefrontal cortex
VTA	Ventral tegmental area

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1 A review of white matter microstructure alterations of pathways of the reward circuit in depression

The work presented in this chapter has been published:

Bracht, T., Linden, D.E., Keedwell, P.A., accepted. A review of white matter microstructure alterations of pathways of the reward circuit in depression. Journal of affective disorders.

The published article has been edited for this chapter. This review article includes results of experimental Chapters 2 and 3, which are essential contributions regarding this topic. Thus, in this chapter I also refer to results that will be described in depth in Chapters 2 and 3.

1.1 Summary

Depressed mood, anhedonia, psychomotor retardation and alterations of circadian rhythm are core features of the depressive syndrome. Its neural correlates can be located within a frontal-striatal-tegmental neural network, commonly referred to as the reward circuit. It is the aim of this chapter to review the literature on white matter microstructure alterations of the reward system in depression. A systematic PUBMED-based search strategy was used. Diffusion tensor imaging (DTI)-studies that have explored neural deficits within the cingulum bundle, the uncinate fasciculus and the supero-lateral medial forebrain bundle/ anterior thalamic radiation - in adolescent and adult depression (acute and remitted), melancholic depression, treatment-resistant depression and those at familial risk of depression -were identified. Thirty-five studies were included. In people at familial risk for depression the main finding was reduced fractional anisotropy (FA) - a putative marker of white matter microstructure - in the cingulum bundle. Both increases and decreases of FA have been reported in the uncinate fasciculus in adolescents. Reductions of FA in the uncinate fasciculus and the anterior thalamic radiation/ supero-lateral medial forebrain bundle during acute depressive episodes in adults were most consistently reported. In conclusion altered cingulum bundle microstructure in unaffected relatives may either indicate resilience or vulnerability to depression. Uncinate fasciculus and supero-lateral medial forebrain bundle microstructure may be altered during depressive episodes in adult MDD. Future studies call for a careful clinical stratification of clinically meaningful subgroups.

1.2 Introduction

1.2.1 Reward system, depression and anhedonia

The reward circuit is central to the experience of pleasure (Haber and Knutson, 2010; Nestler and Carlezon, 2006; Russo and Nestler, 2013). Reward also drives incentive-based learning, appropriate responses to stimuli and goal-directed behaviour (Berridge and Kringelbach, 2008; Grabenhorst and Rolls, 2011; Rushworth et al., 2007). Thus, functionally the reward system is not restricted to hedonic responses but also mediates cognitive planning and motor control. Anatomically, the ventral tegmental area (VTA) and the nucleus accumbens (NAcc) are at the core of the reward circuit. Further key structures include the orbitofrontal cortex (OFC), the anterior cingulate cortex (ACC), the dorsolateral prefrontal cortex (dlPFC), the hypothalamus, the thalamus, the amygdala and the hippocampus (Der-Avakian and Markou, 2012; Haber and Knutson, 2010).

The idea of an anatomically defined reward circuit was based on the finding of Olds and Milner who demonstrated that rats would work to induce electrical stimulation of specific brain regions (Olds and Milner, 1954). Self-stimulation and pharmacological studies have shown that the VTA and the NAcc are the most prominent regions for mediating incentive-based learning (Kelley and Berridge, 2002; Schultz et al., 1997). Further, phylogenetically older structures such as the hypothalamus are crucial for reward-seeking behaviour such as feeding and sexual behaviour (Hikosaka et al., 2008; Nestler and Carlezon, 2006). Reward signals also reliably activate the OFC (Kringelbach and Rolls, 2004; O'Doherty et al., 2001) while the amygdala is essential for the learning of stimulus-reward associations (Baxter and Murray, 2002; Russo and Nestler, 2013). Furthermore, amygdala and hippocampus (via the fornix) project to the NAcc hereby providing important emotional and motivational information (Haber and Knutson, 2010). The hippocampus is thought to play a pivotal role for memory encoding based on the valence of a stimulus (Russo and Nestler, 2013). The dorsal ACC (dACC) and the dlPFC are crucial if working memory is required to evaluate multiple choices of action and to select and initiate the most valuable option (Fletcher and Henson, 2001; MacDonald et al., 2000; Ridderinkhof et al., 2004). We can thus define a core reward circuit, consisting of VTA, NAcc and OFC, and a wider system, incorporating amygdala, hippocampus, dlPFC and dACC which provide crucial functions of memory and evaluation.

The importance of the reward circuit in mediating pleasure has also been clearly demonstrated in positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies in humans. For instance, responses in the reward circuit have been evoked following pleasurable experiences such as eating chocolate (Small et al., 2001), listening to music (Blood and Zatorre, 2001; Menon and Levitin, 2005), application of cocaine (Breiter et al., 1997) and sexual stimulation and orgasm (Holstege et al., 2003; Huynh et al., 2013).

These core regions of the reward circuit function as a complex network and cannot work in isolation (Haber and Knutson, 2010). Failure to successfully involve distinct key regions of the reward circuit may be associated with depressive symptoms in major depressive disorder (MDD) (Nestler and Carlezon, 2006). For instance, depressed mood and anhedonia, the reduced capacity to derive pleasure from previously rewarding experiences may be linked to deficits in reward processing in the VTA-NAcc pathways (Russo and Nestler, 2013; Stoy et al., 2012). Psychomotor retardation could stem from a disturbed interplay in the reward system leading to deficits in appropriate goal-directed behaviour (Bracht et al., 2012a; Der-Avakian and Markou, 2012; Walther et al., 2012b), while extensive ruminating may reflect cognitive deficits to inhibit inappropriate processes based on earlier experiences (Siegle et al., 2002) or intensified expectations of negative outcomes (Rosenblau et al., 2012). Further, disturbances of sleep, appetite, energy levels and circadian rhythms may be related to deficits in the hypothalamus (Hikosaka et al., 2008; Nestler and Carlezon, 2006).

1.2.2 Reward circuitry in depression: cingulum bundle, uncinate fasciculus and medial forebrain bundle

These associations between symptoms of depression and dysfunctions of the reward system have given rise to pathophysiological models implicating functional and structural alterations in the reward circuitry. Indeed, fMRI-studies in depression have demonstrated decreases of subcortical and limbic brain areas of the reward system following pleasant stimuli, while increased activation in cortical areas has been reported (Epstein et al., 2006; Keedwell et al., 2005; Smoski et al., 2009; Zhang et al., 2013). Furthermore, voxel-based morphometry (VBM)-studies indicate grey matter loss in MDD in dlPFC, ACC, OFC and amygdala (Bora et al., 2012; Du et al., 2012; Lai, 2013). Therefore, the search for neurobiological underpinnings of

depressive symptoms such as anhedonia has shifted towards core regions of the reward system such as the VTA and the NAcc e.g. (Blood et al., 2010b; Bracht et al., 2014).

This chapter focuses on the role of the major reward system pathways in depression: the cingulum bundle (CB), the uncinate fasciculus (UF) and the supero-lateral medial forebrain bundle (slMFB). Typical reconstructions of these tracts are shown in Figure 1.1.

CB and UF are the main pathways linking the ventromedial frontal cortex (ACC and OFC) to anterior temporal structures, including the amygdala (UF) and to posterior parietal and temporal cortices (CB) (Bracht et al., 2009; Catani et al., 2002; Keedwell et al., 2012). These pathways are thus important components of the reward system. The role for the ventromedial frontal cortex in processing of diverse and abstract rewards (Gottfried et al., 2003; Kringelbach and Rolls, 2004) and for anhedonia have been clearly demonstrated in structural and functional neuroimaging studies in both healthy controls and in MDD (Harvey et al., 2007; Keedwell et al., 2012; Pizzagalli et al., 2004; Wacker et al., 2009). UF projections from the ventromedial frontal cortex to the amygdala may also play a role in reward-based learning (Baxter and Murray, 2002; Gottfried et al., 2003) and in rumination in MDD (Rosenblau et al., 2012; Siegle et al., 2002).

The MFB is at the core of the reward system, directly connecting the most prominent regions of the reward circuitry, namely VTA, NAcc, OFC and hypothalamus. It has been described extensively in tract-tracing studies in rodents (Geeraedts et al., 1990a, b; Nieuwenhuys et al., 1982; Veening et al., 1982) and in human post-mortem studies (Nieuwenhuys et al., 2008a). It has two branches, the infero-medial MFB (imMFB) and the slMFB. While the imMFB projects from the VTA to the lateral hypothalamus the slMFB travels through the anterior limb of the internal capsule (ALIC) and reaches frontal brain regions (Coenen et al., 2009; Coenen et al., 2012). The slMFB is essential for behaviour that drives activities, supports exploration and mediates emotions like curiosity, excitement and desire (Coenen et al., 2011; Dobrossy et al., 2014). This ensures positive emotional behaviour and has been conceptualized as the SEEKING system within the framework of affective neuroscience (Panksepp, 1998, 2011). The anterior thalamic radiation (ATR) connects the thalamus with prefrontal brain regions. The ATR is located medially to the slMFB; however within the ALIC there is some spatial overlap with the slMFB

that cannot be resolved with currently available resolutions of MRI techniques. In contrast to the slMFB the ATR may rather mediate distress and sadness, conceptualized as the GRIEF system in terms of affective neuroscience (Coenen et al., 2012; Coenen et al., 2011; Panksepp, 2011).

1.2.3 Diffusion Tensor Imaging (DTI)

Diffusion Tensor Imaging (DTI) enables inferences to be made on tissue microstructure *in* vivo. If water diffuses freely in all directions this is called isotropic diffusion. However in the white matter of the brain a series of tissue components such as axons, myelin, glia cells and their respective arrangement amongst each other pose barriers to the mobility of water molecules leading to hindered/ restricted diffusion. In white matter (as opposed to grey matter) there is an orientational difference in the hindrance/ restriction which is described as anisotropic diffusion. The three dimensional diffusivity of water molecules can be modelled using DTI (Basser et al., 1994). Based on the eigenvalue of the diffusion tensor different diffusion properties can be calculated including fractional anisotropy (FA), mean diffusivity (MD), axial and radial diffusivity (AD and RaD). The most common diffusion MRI-based measure for characterization of white matter microstructure is fractional anisotropy (FA). FA-values range between 0 and 1. Zero indicates perfectly isotropic diffusion and 1 indicates perfectly anisotropic diffusion (Basser and Pierpaoli, 1996; Beaulieu, 2002). Although much less frequently reported MD, AD and RaD may complement findings of FA and in conjunction help to interpret potentially underlying tissue microstructure alterations. For instance, studies in dysmyelinated shiverer mice and studies investigating axonal degeneration in both humans and animals (Concha et al., 2006; Song et al., 2003; Song et al., 2002) suggest that AD may be sensitive to axonal pathologies, while RaD may be sensitive to myelination. Thus, these diffusion properties reflect white matter tissue microstructure which in turn could affect functional connectivity within a neural circuit. Nevertheless, given the complexity of brain architecture and the multiple influencing factors on each of the diffusion metrics (e.g. myelination, packing density, axonal diameter, membrane permeability, crossing of fibres or the curvature of the tract of interest), it is currently impossible to draw definite conclusion on specific biological brain alterations using DTI (Jones et al., 2013b).

1.2.4 Tractography vs. whole brain approaches

The analysis of DTI data can be performed for the whole-brain or confined to specific anatomical regions or tracts. Voxel-based analyses (VBA) and tract based spatial statistics (TBSS) (Smith et al., 2006) are automated approaches, comparing diffusion properties such as FA on a voxel-by-voxel level of the whole brain, following spatial normalization of FA images. While VBA compares whole voxels between groups, TBSS confines its analyses to a thinned white matter skeleton. Many researchers favor TBSS approaches over VBA approaches due to the more accurate spatial alignment of the voxels of the brain and the somewhat arbitrary filter size of smoothing applied in VBA-studies (Abe et al., 2010; Jones et al., 2005). Conversely, region of interest (ROI)-approaches and tractography studies investigate anatomically pre-defined brain regions. Tractography studies allow for an *in vivo* reconstruction of specific pathways of the brain and provide a greater degree of tract-specific anatomical validity than ROI-approaches (Kanaan et al., 2006) because individual differences of fibre pathways can be taken into account by manual delineation of seed regions (Catani et al., 2002). Further, tractography studies enable a more reliable allocation of findings of group differences to specific pathways than voxel-based approaches. This must be the case because there is crossing of fibre populations in about 90% of the voxels (Jeurissen et al., 2013). Therefore allocation of isolated voxels to specific pathways can be highly speculative using whole brain voxel-based analyses (Frodl et al., 2012; Keedwell et al., 2012).

1.2.5 Previous reviews and conceptual considerations

Previous reviews and meta-analyses of diffusion-MRI studies point to reduced FA in the left superior longitudinal fasciculus (Murphy and Frodl, 2011), the genu of the corpus callosum (Wise et al., 2015), bilateral frontal lobe, right fusiform gyrus and right occipital lobe (Liao et al., 2013) and frontal and temporal lobes (Sexton et al., 2009). However, crucial difficulties of meta-analyses include the grouping of heterogeneous populations (which may anatomically differ from each other) and application of different data acquisition schemes and imaging analyses methods (which may lead to different results) (Sexton et al., 2009). With a recent increase of tractography studies showing different results than voxel-based approaches (Bracht et al., 2015a; Frodl et al., 2012; Keedwell et al., 2012) the latter point becomes in particular important.

A further source of heterogeneity in neuroimaging findings in depression may be due to differences in clinical presentations. In the search for trait biomarkers of MDD, diffusion MRI studies have not only included acutely ill MDD patients, but also patients in remission and individuals at risk of depression by virtue of their family history. Furthermore, some studies have explored the influence of treatment-resistance and severity (Serafini et al., 2014). For example, melancholic depression, which is characterized by severe anhedonia, a different quality of sadness and marked vegetative symptoms (Rush and Weissenburger, 1994), may be associated with pathology localized in different or additional brain regions when compared to non-melancholic depression (Bracht et al., 2014; Korgaonkar et al., 2011; Pizzagalli et al., 2004).

Therefore, in this chapter DTI-findings in the core pathways of the reward system are separately discussed for those at familial risk for depression, patients with adolescent depression and patients with adult depression (depressed, remitted, treatment-resistant, melancholic and non-melancholic). We include tractography studies that investigated the CB, UF or slMFB. We also report findings of whole brain voxel-based analyses (VBA and TBSS-studies) and ROI-studies provided that the identified alterations in voxels, being localized along the anatomical course of CB, UF or slMFB.

1.3 Method

1.3.1 Search strategy

The relevant diffusion MRI literature was identified using PUBMED (http://www.ncbi.nlm.nih.gov/pubmed) in March 2015. The database was searched using the following Boolean strategy: (DTI OR diffusion tensor imaging OR white matter OR tractography OR fibre tracking) AND (depression OR depressive OR remission OR remitted OR unipolar) AND (orbitofrontal OR dorsolateral prefrontal OR amygdala OR hippocampus OR brain stem OR midbrain OR ventral tegmental area OR nucleus accumbens OR ventral striatum OR thalamus OR limbic OR reward OR anterior limb OR uncinate OR medial forebrain bundle OR anterior thalamic radiation OR fornix OR parahippocampal OR cingulum).

Reference lists of PUBMED-identified studies were then searched for additional relevant studies. Studies were included if they used DTI-based diffusion indices (FA, MD, AD or RaD) to compare major depressive disorder (MDD) with healthy control subjects. We also included studies focusing on subjects at risk for developing MDD. Studies of bipolar disorder and late life depression were excluded because these disorders differ in clinical presentation and presumably pathophysiology from major depression. Further, studies investigating depression as comorbidity of other disorders (e.g. AIDS, Parkinson's disease) were excluded. Further exclusion criteria were comorbid substance abuse and neurological disorders (including mild cognitive impairment and dementia).

1.4 Results

A total of 35 publications were in included (see table 1.1). The results are organized according to subgroups of individuals with familial risk of MDD, adolescents with acute depression, adults with MDD (acute and remitted), treatment-resistant depression and melancholic-MDD.

Further, we display results of tractography studies comparing diffusion properties of MDD-patients with healthy controls for the main reward system tracts: CB, UF and slMFB (Table 1.2, Figure 1.1). In Table 1.2 we also include VBA, TBSS and ROI-studies that identified alterations of diffusion properties in the ALIC, because this region likely incorporates slMFB/ ATR fibre tracts (Figure 1.1). We further include findings of VBA and TBSS studies being localized within the CB and the UF.

Study	Methods	Participants	Results
At familial risk for depression			
(Frodl et al., 2012)	3 Tesla 61 directions TBSS Tractography (UF, fornix)	21 HR (38.1 ± 14.5) 24 HC (34.7 ± 11.0)	Increased FA in the right fornix in HR. Negative finding for UF. MD, RaD and AD did not differ between groups.
(Huang et al., 2011)	3 Tesla 30 directions TBSS (voxel-wise and tract-level analysis)	18 HR (15.7 ± 2.3) 13 HC (15.5 ± 3.0)	Decreased FA in the left CB and left and right UF
(Keedwell et al., 2012)	3 Tesla 30 directions Tractography (UF, CB) TBSS	18 HR (22.2) 15 HC (22.1)	Decreased FA in left and right CB. No differences of AD. RaD was significantly higher in HR in the CB. Negative finding for UF. Negative finding with TBSS
Adolescent depression			
(Aghajani et al., 2013)	3 Tesla 32 directions TBSS Region of interest	25 MDD (15.6 ± 1.4) 21 HC (14.7 ± 1.6)	Increased FA in the UF. Higher AD, lower RaD and preserved MD
(Bessette et al., 2014)	3 Tesla 12 directions TBSS	31 MDD (17.1 ± 2.4) 31 HC (17.0 ± 2.4)	Decreased FA in bilateral frontal lobe, bilateral ALIC, bilateral midbrain, right ATR
(Cullen et al., 2010)	3 Tesla 30 directions TBSS Tractography	14 MDD (16.8 ± 1.3) 14 HC (16.8 ± 1.5)	Decreased FA in the right UF Negative finding for CB
(Henderson et al., 2013)	3 Tesla 12 directions TBSS	17 MDD (16.8 ± 2.2) 16 HC (16.4 ± 1.4)	Decreased FA in the right CB (posterior parts near the precuneus)
(LeWinn et al., 2014)	3 Tesla 30 directions Tractography TBSS	52 MDD (16 ± 0.2) 42 HC (16 ± 0.2)	Decreased FA in bilateral UF. Higher RaD in bilateral UF. No changes of AD. No significant differences in CB
Remitted depression			
(Arnold et al., 2012)	1.5 Tesla 30 directions VBA ROI approach Probabilistic fibre tracking	17 RD (30.4 ± 1.4) 21 HC (26.9 ± 7.8)	Increased FA and decreased MD in the left amygdala (grey matter). Increased MD in the PFC. No significant whole brain differences of VBA-analyses.
(Bracht et al., 2015)	3 Tesla 60 Directions Tractography	18 RD (22.4 ± 3.6) 22 HC (22.5 ± 4.5)	No group differences with either tractography or TBSS. Association between hedonic tone and FA of

			the left slMFB
(de Diego-Adelino et al., 2014)	3 Tesla 15 directions TBSS	15 RD (47 ± 9.4) 17 HC (43.4 ± 11.4)	No group differences between RaD and HC.
Depressed			
(Abe et al., 2010)	1.5 Tesla Number of directions not stated VBA	21 MDD (48 ± 13.5) 42 HC (48 ± 13.2)	Increased MD in bilateral parahippocampal gyri, hippocampus, left temporal lobe, bilateral frontal lobe
(Blood et al., 2010)	3 Tesla 6 directions ROI	MDD (36.3 ± 12) HC (35.3 ± 11)	Increased FA in the right VTA Decreased FA in the dlPFC
(Carballedo et al., 2012)	3 Tesla 61 directions Fibre tracking (UF, Fornix, CB)	37 MDD (40.4 ± 10) 42 HC (36.3 ± 13)	Patients carrying the BDNF-met-allele had decreased FA in the UF compared to those patients homozygous for val-allele and compared to healthy subjects carrying the met-allele.
(Guo et al., 2012b)	1.5 Tesla 13 directions TBSS	22 MDD (28.1 ± 9.9) 19 HC (24.4 ± 4.2)	Decreased FA in bilateral ALIC and frontal lobe
(Jia et al., 2014)	3 Tesla 15 directions Tractography	63 MDD 46 HC	Decreased FA in MDD in the ATR, more pronounced in MDD patients with suicide attempt
(de Kwaasteniet et al., 2013)	3 Tesla 32 directions Tractography	18 MDD (44.6 ± 10.4) 24 HC (40.2 ± 13.1)	Decreased FA in bilateral UF
(Lai and Wu, 2014)	3 Tesla 30 directions TBSS	44 MDD (36.9 ± 5.3) 27 HC (38.3 ± 11.8)	Decreased FA and decreased AD in the right ATR
(Li et al., 2007)	1.5 Tesla 13 Directions ROI	19 MDD (28.1 ± 7.4) 20 HC (26.7 ± 6.9)	Decreased FA in the frontal cortex
(Ma et al., 2007)	1.5 Tesla 13 Directions VBA	14 MDD (28.9 ± 8.0) 14 HC (27.1 ± 6.7)	Decreased FA in right middle frontal gyrus
(Murphy et al., 2012)	3 Tesla 61 directions TBSS	45 MDD 45 HC (37 ± 12.8)	Decreased FA in the CB, left and right UF
(Seok et al. 2013)	20 directions TBSS	86 MDD (44) 62 HC (42)	Decreased FA in the left CB and bilateral frontal white matter
(Song et al., 2014)	3 Tesla 42 directions Tractography	95 MDD (31.5) 34 HC (33.8)	Decreased FA in the right solitary tract (amygdala, brain stem). No significant differences for MD, AD, RaD. No differences in the

			nigrostriatal tract and the CST.
(Steele et al., 2005)	1.5 Tesla 6 Directions VBA	15 MDD (46) 14 HC (43)	Decreased FA in the right temporal lobe Decreased FA in UF
(Ouyang et al., 2011)	1.5 Tesla 13 directions VBA	18 MDD (27.4 ± 6.4) 18 HC (27.0 ± 6.0)	Decreased FA in frontal, temporal lobe and cingulum
(Tha et al., 2013)	1.5 Tesla 12 directions VBA	19 MDD (38.6 ± 13) 19 HC (36.5 ± 12.5)	Decreased FA in bilateral frontal white matter, ALIC. No differences in MD.
(Walther et al., 2012)	3 Tesla 42 directions VBA	21 MDD (41 ± 13.7) 21 HC (45 ± 13.7)	Decreased FA in left ATR
(Wu et al., 2011)	1.5 Tesla 13 directions VBA	23 MDD (31.4 ± 8.8) 21 HC (30.4 ± 8.2)	Decreased FA in the right frontal lobe. Increased apparent diffusion coefficient (ADC)
(Zhang et al., 2012)	3 Tesla 32 Directions Tractography	21 MDD (47.7 ± 10.15) 21 HC (48.3 ± 14.3)	Decreased FA and increased RaD in the right UF Negative finding for the CB
(Zhu et al., 2011)	1.5 Tesla 13 directions TBSS	25 MDD (20.5 ± 1.86) 25 HC (20.33 ± 1.68)	Decreased FA in the left ALIC and right PHC
(Zou et al., 2008)	3 Tesla 15 directions VBA	45 MDD (33.2 ± 8.9) 45 HC (31.0 ± 10.3)	Decreased FA in the left ALIC
Treatment-resistant			
(de Diego-Adelino et al., 2014)	3 Tesla 15 directions TBSS	18 TRD (48.5 ± 7.3) 17 HC (43.4 ± 11.4)	Decreased FA in treatment-resistant MDD in the bilateral cingulum and the left VMPFC compared to HC, first-episode and to RD
(Guo et al., 2012a)	TBSS	23 TRD (27.4 ± 7.7) 19 HC (24.4 ± 4.2)	Decreased FA in the right ALIC
(Peng et al., 2013)	3 Tesla 30 directions VBA	30 TRD (26.8 ± 5.2) 25 HC (28.2 ± 4.9)	Decreased FA in the left middle frontal gyrus Left temporal lobe
Melancholic depression			
(Bracht et al., 2014)	3 Tesla 42 directions Fibre tracking (infero-medial MFB, supero-lateral MFB)	22 MDD (44.8 ± 14) 21 HC (41.4 ± 14)	No difference between all MDD and HC Decreased FA in right slMFB (VTA-OFC and VTA-dlPFC connections) in the melancholic subgroup
(Korgaonkar et al., 2011)	3 Tesla 42 directions	29 MDD (40.5 ± 15.8)	No group difference comparing all MDD

	TBSS	39 HC (29.6 ± 12.7)	patients with HC. Decreased FA in the fornix/ stria terminalis, dlPFC, frontal, temporal regions in the melancholic subgroup

Table 1.1 Overview of included studies

Abbreviations: HR, healthy relatives; HC, healthy controls; MDD, major depressive disorder (acute depression); RD, remitted depressed; TRD, treatment-resistant depression; TBSS, tract based spatial statistics; VBA, voxel-based analyses; ROI, region of interest; FA, fractional anisotropy; MD, mean diffusivity; RaD, radial diffusivity; AD, axial diffusivity; UF, uncinate fasciculus; CB, cingulum bundle; slMFB, supero-lateral medial forebrain bundle; ATR, anterior thalamic radiation; ALIC, anterior limb of the internal capsule; ACC, anterior cingulate cortex; VTA, ventral tegmental area; OFC, orbitofrontal cortex; PFC, prefrontal cortex; dlPFC, dorsolateral prefrontal cortex; VMPFC, ventromedial prefrontal cortex, BDNF, brain-derived neurotrophic factor.

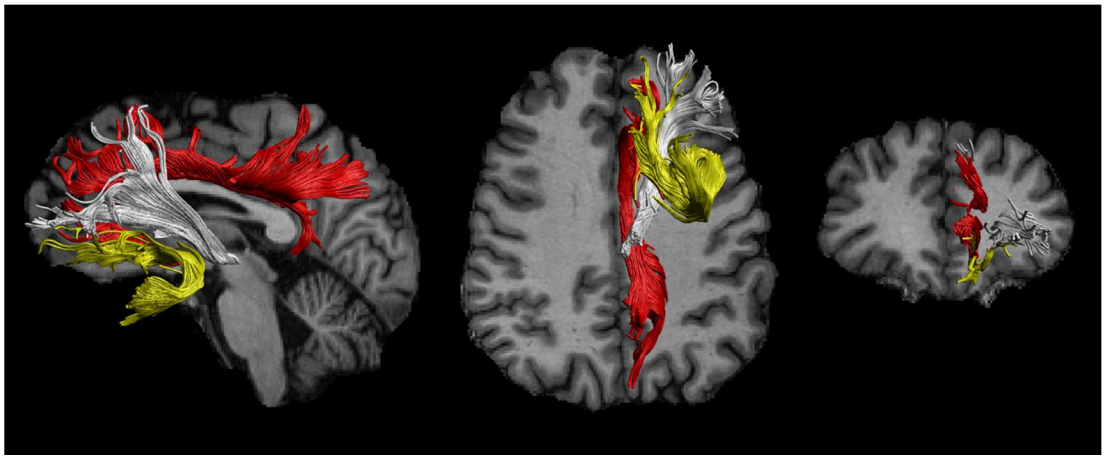

Figure 1.1 Typical reconstructions of CB, UF and slMFB

Typical reconstructions of the cingulum bundle (CB, red), uncinate fasciculus (UF, yellow) and supero-lateral medial forebrain bundle (slMFB, white) are shown,

At familial risk for depression		Adolescent depression		Adult depression	
Cingulum Bundle					
Group differences	**No group differences**	**Group differences**	**No group differences**	**Group differences**	**No group differences**
(Huang et al. 2011 ; Keedwell et al. 2012)		(Henderson et al. 2013)	(Cullen et al. 2010 ; LeWinn et al. 2014)	(de Diego-Adelino et al. 2014; Murphy et al. 2012; Ouyang et al. 2011; Seok et al. 2013)	(Carballedo et al. 2012; Zhang et al. 2012)
Uncinate Fasciculus					
Group differences	**No group differences**	**Group differences**	**No group differences**	**Group differences**	**No group differences**
(Huang et al. 2011)	(Frodl et al. 2012 ; Keedwell et al. 2012)	(Aghajani et al. 2013 ; Cullen et al. 2010; LeWinn et al. 2014)		(Carballedo et al. 2012; de Kwaasteniet et al. 2013; Murphy et al. 2012; Steele et al. 2005; Zhang et al. 2012)	
Supero-lateral medial forebrain bundle/ anterior thalamic radiation/ anterior limb of the internal capsule					
Group differences	**No group differences**	**Group differences**	**No group differences**	**Group differences**	**No group differences**
		(Bessette et al. 2014)		(Bracht et al. 2014; Guo et al. 2012a; Guo et al. 2012b; Jia et al. 2014; Lai and Wu 2014; Tha et al. 2013; Walther et al. 2012 ; Zhu et al. 2011; Zou et al. 2008;)	(Bracht et al. 2015a; Song et al. 2014)

Table 1.2 Results of findings of the CB, UF and slMFB

Findings of tractography studies of the cingulum bundle (CB), uncinate fasciculus (UF) and supero-lateral medial forebrain bundle (slMFB) stratified according to the presence of group differences of diffusion properties between MDD and a healthy control group. VBA and TBSS studies with findings along the anatomical course of these tracts are also displayed.

1.5 Discussion

Overall, findings of CB, UF and slMFB microstructural alterations suggest a distinct pattern of pathways that may serve as state or trait marker for depression. Reduced FA in the CB has been reported in unaffected relatives (Huang et al., 2011; Keedwell et al., 2012). However, reports of CB microstructure alterations are inconclusive during acute depression in both adolescent and adult MDD (Carballedo et al., 2012; Cullen et al., 2010; de Diego-Adelino et al., 2014; Henderson et al., 2013; LeWinn et al., 2014; Murphy et al., 2012; Ouyang et al., 2011; Seok et al., 2013; Zhang et al., 2012). There is compelling evidence for reduced FA in the UF in acute depression in adults (Carballedo et al., 2012; de Kwaasteniet et al., 2013; Murphy et al., 2012; Steele et al., 2005; Zhang et al., 2012); evidence in adolescents is emerging as well, although fewer studies and FA changes in opposing directions have been published (Aghajani et al., 2013; Cullen et al., 2010; LeWinn et al., 2014). First results indicate slMFB microstructure alterations in melancholic MDD (Bracht et al., 2014), but not in remitted MDD/ non-melancholic MDD (Bracht et al., 2015a; Bracht et al., 2014; Song et al., 2014). A series of VBA and TBSS studies have reported reduced FA in the ALIC and in the frontal lobe in acute depression, regions that may be in incorporated in UF and slMFB/ ATR.

1.5.1 Cingulum Bundle

Two family history studies suggest that reduced FA of the CB may represent a biomarker of vulnerability in MDD (Huang et al., 2011; Keedwell et al., 2012). Furthermore, FA was negatively related to trait anhedonia (Keedwell et al., 2012). If reductions in CB FA truly represent a marker of vulnerability for depression, one would expect to observe such changes in acute MDD as well.

In adolescent depression one group indeed reported decreased FA in posterior parts of the cingulum (Henderson et al., 2013). However, results were not corrected for multiple comparisons. In contrast two tractography studies have reported negative findings in acute adolescent depression (Cullen et al., 2010; LeWinn et al., 2014). Therefore, to date there is no conclusive evidence for cingulum bundle microstructural alterations in adolescents during depressive episodes.

Similarly, results for acute MDD in adults are inconsistent. Reduced FA was found in the CB in treatment-naïve adult MDD (Ouyang et al., 2011) and acute depression (Seok et al., 2013). Further, reductions of FA in bilateral cinguli were reported in treatment-resistant MDD (de Diego-Adelino et al., 2014). However, no changes in FA were demonstrated in the whole CB in adults (Zhang et al., 2012), or its sub-regions (Carballedo et al., 2012).

So far three studies have investigated effects of specific genetic variants on cingulum microstructure in depression. In a genetic imaging study, FA reductions in the cingulum in adult MDD were found to be driven by a subgroup homozygous for the A allele of a common single-nucleotide polymorphism (SNP) at position (rs11140714) of the neurotrophic tyrosine kinase gene (Murphy et al., 2012). Increased FA was observed in carriers of the met-allele of the SNP at position (rs6265) of the brain-derived neurotrophic factor (BDNF) gene in the left rostral cingulum compared to those homozygous for the val-allele, although this finding was not specific for MDD-patients (Carballedo et al., 2012). (Seok et al., 2013) identified lower FA in the right parahippocampal cingulum in a depressed group homozygous for the valine COMT val158met polymorphism compared to a depressed group of methionine carrier subjects.

Thus, based on findings in unaffected relatives, reduced FA in the CB may indicate genetic vulnerability for depression (Huang et al., 2011; Keedwell et al., 2012). However, given that in acute depressive episodes in both adolescents and adults several studies did not report any FA changes an alternative explanation for reduced FA in unaffected relatives may be that CB microstructure represents a structural correlate of resilience. In that case remodeling of CB microstructure may lead to a loss of resilience and in fact increase the risk for developing depression.

Divergent findings in the cinguli within and across subgroups of patients with depression may also be owed to variations in the degree of treatment naivety between and within studies (Ouyang et al., 2011) and treatment-resistance (de Diego-Adelino et al., 2014). It is possible, that CB microstructure alterations are only present in those specific subgroups. In addition, studies suggest that genetic factors (Carballedo et al., 2012; Murphy et al., 2012; Seok et al., 2013) may be associated with specific changes in the cingulum. These are crucial factors to take into account in future studies. Further, it seems prudent to use tractography to disentangle different sub-compartments of the CB (e.g. the subgenual CB or the

parahippocampal cingulum) since white matter microstructure alterations may only be present and detectable in sub-compartments of this large fibre bundle (Bracht et al., 2015b; Carballedo et al., 2012; Jones et al., 2013a). The acute or chronic effects of treatment on CB-FA are not known. It is possible that subtle changes in the CB are remediated by antidepressant treatment in the short and long term. Longitudinal treatment studies would therefore be informative. First studies point to plastic white matter changes of the CB during the time course of clinical remission (Bracht et al., 2015b). Further studies of the relationship between cingulum microstructure and clinical states may also shed light on the mechanism behind the well-documented antidepressant effect of surgical cingulotomy (Ballantine et al., 1987; Linden, 2014).

1.5.2 Uncinate Fasciculus

In adolescents both increases (Aghajani et al., 2013) and decreases (Cullen et al., 2010; LeWinn et al., 2014) in uncinate FA have been reported. Decreases in FA have been consistently found in depressed adults (Carballedo et al., 2012; de Kwaasteniet et al., 2013; Murphy et al., 2012; Steele et al., 2005; Zhang et al., 2012), but not in young people at risk of depression (Frodl et al., 2012; Keedwell et al., 2012). Thus, based on the finding of increased FA in the UF in adolescents (Aghajani et al., 2013) it is possible, that microstructural alterations in acute adolescent depression differ from those in adults. This difference may be owed to an age-dependency of neuroplastic processes (Blumenfeld-Katzir et al., 2011; Bracht et al., 2015b). However, decreases in FA have also been reported (Cullen et al., 2010; LeWinn et al., 2014). Therefore, reliable conclusions regarding the directionality of FA changes in adolescents cannot be drawn. Replication studies stratifying patients according to clinical presentation, medication status and comorbidities may shed further light on factors associated with microstructural UF alterations in adolescents.

Further support for microstructural alterations of the UF in MDD arises from VBA and TBSS-based observations of reduced FA in frontal and temporal brain regions, likely incorporating the UF (Sexton et al., 2009). Reduced FA in frontal regions has been reported during depressive episodes in adolescents (Bessette et al., 2014) and in adults (Ouyang et al., 2011; Tha et al., 2013; Wu et al., 2011), in first episode treatment-naïve MDD patients (Li et al., 2007; Ma et al., 2007), melancholic-MDD patients (Korgaonkar et al., 2011) and treatment resistant MDD-patients (de Diego-Adelino et al., 2014; Peng et al., 2013). Similarly, decreases of FA were found in the temporal lobe in adult MDD (Ouyang et al., 2011; Steele et al., 2005; Zhu et al.,

2011), melancholic-MDD (Korgaonkar et al., 2011) and treatment resistant MDD (Peng et al., 2013).

In summary, a number of independent studies suggest that FA in the UF is reduced in adult depression, while in adolescent depression both increases and decreases have been reported. There is a lack of convincing evidence that UF microstructure is altered in at risk populations. Hence, the current data suggest that this disturbance is state dependent.

1.5.3 Supero-lateral medial forebrain bundle

One tractography study has reported reduced FA in the slMFB in melancholic but not in non-melancholic MDD-patients or in all MDD-patients (Bracht et al., 2014). In line with this finding a further tractography study of a large sample of acutely depressed MDD patients did not find alterations of FA in VTA-NAcc connection pathways (Song et al., 2014). It would be of great interest to investigate if group differences in this large sample might emerge in a comparison of healthy participants with a subset of those MDD-patients meeting criteria for melancholic depression (Bracht et al., 2014; Korgaonkar et al., 2011).

Besides a distinct quality of depressed mood melancholic depression is characterized by psychomotor retardation, reduced appetite and worsening of mood typically in the morning (Rush and Weissenburger, 1994). While the latter may be linked to slMFB projections from the VTA to the hypothalamus which is essential for feeding behaviour and circadian rhythm (Hikosaka et al., 2008; Nestler and Carlezon, 2006), the former may well be conceptualized within the framework of affective neuroscience (Panksepp, 1998). According to this concept the slMFB is essential for the SEEKING system that mediates exploring behaviour (Coenen et al., 2011; Dobrossy et al., 2014). Therefore, deficits in exploring behaviour captured as psychomotor retardation in melancholic depression may well underlie alterations in structural connectivity of slMFB pathways (Bracht et al., 2014).

No changes in FA were found in the sole tractography study investigating imMFB/ slMFB microstructure in remitted depression (Bracht et al., 2015a). In the same study, a negative correlation between FA and hedonic tone was identified across all participants (Bracht et al., 2015a). This finding in humans is supported by compelling evidence in rodents that clearly indicate the relevance of the slMFB for

reward SEEKING behaviour (Olds and Milner, 1954; Russo and Nestler, 2013; Schultz et al., 1997).

Further indirect support for an involvement of the slMFB in severe/ treatment-resistant depression is provided by invasive therapeutic trials targeting the slMFB: Tractography guided deep brain stimulation (DBS) of the slMFB led to rapid symptomatic improvements in treatment-resistant depression (Schlaepfer et al., 2014; Schlaepfer et al., 2013a). High response rates and improvements in functioning in the absence of significant side effects were reported (Galvez et al., 2015). Moreover, anterior capsulotomy, a surgical approach that places lesions in the ALIC, in completely treatment-refractory patients led to convincing improvements in a majority of patients (Christmas et al., 2011). Further indirect evidence for a role of the slMFB in depression stems from research in neurodegenerative disorders such as Parkinson's disease (PD). Comparing a group of depressed PD with non-depressed PD-patients reductions of FA were found in regions incorporating the slMFB in the depressed PD-patient group (Huang et al., 2014). Thus neurodegenerative processes of the slMFB may be associated with depressive symptoms.

In addition, a series of voxel based studies have reported reduced FA in acute depressive episodes, in first-episode, treatment resistant and melancholic depression in both the ALIC and in frontal brain regions (de Diego-Adelino et al., 2014; Guo et al., 2012; Korgaonkar et al., 2011; Peng et al., 2013; Tha et al., 2013; Walther et al., 2012b; Zhu et al., 2011; Zou et al., 2008). These findings may well reflect white matter microstructure alterations of the slMFB However, due to substantial crossing of different fibre populations, allocation of isolated voxels to specific fibre tracts can be highly speculative. For instance, the ATR is localized medially albeit spatially overlapping with the slMFB (Coenen et al., 2012). These two pathways thus cannot be reliably disentangled with voxel-based approaches. One tractography study of the ATR has reported reduced FA in depression (Jia et al., 2014). Further tractography studies are called for to explore the differential role of ATR/ slMFB in depression symptomatology. Ideally, novel fibre tracking techniques e.g. (Dell'acqua et al., 2010; Jeurissen et al., 2013) should be applied because these methods are more accurate in regions of crossing fibres (Jeurissen et al., 2013).

In summary, one tractography study points to microstructural alterations of the slMFB in melancholic depression (Bracht et al., 2014). Based on findings localized along the anatomical course of the slMFB, VBA and TBSS studies are suggestive for slMFB alterations in acute (Tha et al., 2013; Walther et al., 2012b; Zhu et al., 2011; Zou et al., 2008) and treatment-resistant depression (de Diego-Adelino et al., 2014; Guo et al., 2012; Peng et al., 2013) as well. So far, there is no evidence for microstructural alterations of the slMFB during remitted depression (Bracht et al., 2015a). Given the negative finding in remitted depression, slMFB microstructure may undergo neuroplastic processes during remission and therefore serve as a state rather than as a trait marker. Longitudinal studies are required to explore this possibility. Another explanation is that medication effects may induce structural changes in the slMFB and remediate structural alterations that can be observed in severe depression.

1.5.4 The effect of medication

Out of the 35 studies included in the review, 19 investigated unmedicated or treatment-naïve patients and have reported significant group differences. This strongly supports the assumption that brain changes of white matter identified in depression are associated with the disease process rather than being mere effects of medication. Bessette et al. compared medicated with unmedicated patients and found no group differences of FA between the two groups (Bessette et al., 2014). De Diego-Adelino and colleagues controlled for medication effects that did not alter the results (de Diego-Adelino et al., 2014). Some of the tractography studies investigating medicated patients used comparison tracts or investigated multiple tracts and identified FA-changes localized in specific tracts that contradict the assumption of a global effect of medication on brain structure e.g.(Bracht et al., 2014; Cullen et al., 2010). On the other hand, successful anti-depressive treatment may reverse changes in FA (Bracht et al., 2015b). In bipolar disorder one study suggested that lithium is associated with increased FA (Benedetti et al., 2011), while another study points to mood stabilizers reducing FA (Versace et al., 2008). However, based on cross-sectional approaches the question of medication effects on white matter microstructure cannot be addressed. Longitudinal interventional studies including both medicated and unmedicated patients are required to more reliably address this issue.

1.5.5 Implications of differences in methodological approaches

Six studies in this review have used both tractography and whole brain voxel-based approaches. Four out of these six studies found significant group differences or correlations using tractography while significance was not reached using whole brain voxel-based approaches (Bracht et al., 2015a; Bracht et al., 2014; Cullen et al., 2010; Keedwell et al., 2012). Therefore, tractography studies may be more sensitive than voxel-based studies in terms of identifying tract specific group differences. However, one tractography study found overlapping results in some of the tracts investigated (Frodl et al., 2012) and a further study found perfectly corresponding results using tractography and TBSS (LeWinn et al., 2014). On the other hand whole-brain voxel-based approaches may detect group differences in additional, unexpected anatomical brain regions and therefore provide important additional information (Cullen et al., 2010; Frodl et al., 2012; LeWinn et al., 2014). Thus, tractography and whole brain approaches may successfully complement each other. Ideally future studies should incorporate both kinds of approaches for analyses of their data. Twelve out of the 35 studies did not only report changes of FA but also of AD, RaD and MD which may further corroborate the presence of putative white matter microstructure alterations.

1.5.6 Limitations

Firstly, a selective overview of white matter changes in reward system pathways is provided. Alterations in other tracts have been observed in MDD (e.g. the superior longitudinal fasciculus and likely contribute to depression symptomatology as well (Murphy and Frodl, 2011). Moreover, fronto-limbic pathways such as the UF and CB are implicated in further processes of relevance to depression such as regulation of negative emotion and cognitive control. It is beyond the scope of this chapter to cover these clinically very relevant issues. Secondly, owing to the small numbers of studies in most of the clinical subgroups, a quantitative meta-analysis has not been conducted. It is a central goal of this review to stratify findings according to clinically meaningful homogeneous subgroups (e.g. (Bracht et al., 2014; de Diego-Adelino et al., 2014; Korgaonkar et al., 2011)). We report both results of tractography studies and whole brain voxel-based approaches, which have been shown repeatedly to yield different results (Abe et al., 2010; Bracht et al., 2014; Cullen et al., 2010; Kanaan et al., 2006; Keedwell et al., 2012). Given the sparse current literature of tractography studies in depression and the diverse clinical subgroups it is currently

not possible to conduct a meaningful meta-analysis. However, this seems prudent once more clinically and methodologically comparable tractography studies have been published. Thirdly, a publication bias towards positive findings cannot be ruled out and more replication studies are required using consistent methods and similar study populations. It is possible that publication bias has exaggerated the relative importance of white matter microstructure in the pathogenesis of MDD.

1.5.7 Summary and future directions

This review focused on diffusion MRI studies investigating white matter microstructure of the reward system. Reduced CB FA may represent a state marker for MDD (Huang et al., 2011; Keedwell et al., 2012), but further investigation is required in medication naïve adults with MDD: changes in the CB might be reversed by treatment (Bracht et al., 2015b). UF (Carballedo et al., 2012; de Kwaasteniet et al., 2013; Murphy et al., 2012; Steele et al., 2005; Zhang et al., 2012) and slMFB microstructure (Bracht et al., 2014) may be altered during depressive episodes in adult MDD, while the latter might be particularly affected in severe depression (Bracht et al., 2014; de Diego-Adelino et al., 2014; Guo et al., 2012; Peng et al., 2013).

Associations between microstructural changes in the major tracts of the reward system and MDD do not, in themselves, prove a functional contribution towards the development of depressionôs core symptoms. The functional significance of these findings needs further investigation by exploring correlations with reward processing performance and symptom profiles (including anhedonia, psychomotor retardation) (Bracht et al., 2015a; Keedwell et al., 2012; Walther et al., 2012b).

Heterogeneity in reported results highlights the importance to carefully select clinically well-defined subgroups of depression (e.g. adolescent depression, melancholic depression, treatment-resistant depression). Further, due to spatial overlap of various pathways within a single voxel, tractography approaches are required to link findings to specific pathways of interest. Ideally, tractography methods that are partly able to resolve ñcrossing fibresò should be applied (Dell'acqua et al., 2010; Jeurissen et al., 2013). The difficulty of disentangling ATR and slMFB fibres in the ALIC is just one example where such approaches should be beneficial.

More research is also needed for a more precise histological interpretation of DTI parameters. Alterations of FA are generally interpreted as indicating microstructural changes of white matter. Histological post-mortem studies of patients with depression suggest reduced glial cell density, reduced dendritic branching and reduced white matter volume (Russo and Nestler, 2013). However, DTI-based measures are unspecific regarding the underlying neurobiology of white matter changes (Jones et al., 2013b). Emerging sub-compartment specific white matter mapping techniques (e.g. methods assessing myelination and axonal diameter) are required to further elucidate the nature of these changes (Assaf and Basser, 2005; Deoni et al., 2008a) and may open exciting new possibilities for an *in vivo* assessment of specific neurobiological changes in depression.

2 Hedonic tone is associated with left supero-lateral medial forebrain bundle microstructure

The work presented in this chapter has been published:

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The published article has been edited for this chapter in order to include additional results and to avoid repetition across Chapter 1. However, this chapter partly covers background information already dealt with in Chapter 1.

I acknowledge Amie Doidge for recruiting, testing and scanning participants.

2.1 Summary

The medial forebrain bundle (MFB) is an important pathway of the reward system. Two branches have been described using diffusion magnetic resonance imaging (MRI)-based tractography: the infero-medial MFB (imMFB) and the supero-lateral MFB (slMFB). Previous studies point to white matter microstructural alterations of the slMFB in major depressive disorder (MDD) during depressive episodes. To extend this finding, this study investigates whether white matter microstructure is also altered in MDD patients that are in remission. Further, we explore associations between diffusion MRI-based metrics of white matter microstructure of imMFB, slMFB and hedonic tone, the ability to derive pleasure. Eighteen remitted depressed (RD) and 22 never depressed (ND) participants underwent high angular resolution diffusion weighted imaging (HARDI) scans. Using the damped Richardson Lucy (dRL) algorithm for the first time the two segments of the two pathways of the MFB (imMFB and slMFB) are reconstructed separately. Mean fractional anisotropy (FA) was sampled along the tracts. Mean-FA of imMFB, slMFB and a comparison tract (the middle cerebellar peduncle) did not differ between ND and RD. Hedonic capacity correlated negatively with mean-FA of the left slMFB, explaining 21% of the variance in mean-FA. Diffusion MRI-based metrics of white matter microstructure of the MFB in RD do not differ from ND. Hedonic capacity is associated with altered white matter microstructure of the slMFB.

2.2 Introduction

The MFB is the central pathway of the reward system and mediates feelings and expectations of pleasure (Coenen et al., 2011; Schultz et al., 1997). Traditionally the MFB was described as an assembly of loosely arranged, thin fibres extending from the septal area. Fibres traverse the lateral preoptico-hypothalamic area and proceed to the tegmentum of the midbrain (Nieuwenhuys et al., 2008b). Coenen et al. were the first to reconstruct the MFB using diffusion MRI-based fibre tracking (Coenen et al., 2009). In addition to this infero-medial MFB (imMFB) branch, the researchers described a supero-lateral branch (slMFB) proceeding from the VTA to the forebrain and the frontal lobe (Coenen et al., 2009; Coenen et al., 2012).

Anhedonia, the reduced capacity to derive pleasure from previously rewarding experiences, is a core feature of MDD. Given its prominent role in the reward system (Nestler and Carlezon, 2006; Schultz et al., 1997), the MFB has become a major focus in the search for the neurobiological underpinnings of MDD (Blood et al., 2010a; Bracht et al., 2014).

Diffusion MRI allows white matter microstructure to be probed by indirectly measuring the hindrance of diffusion of water molecules (Basser et al., 1994). The most commonly used diffusion MRI-based measure in clinical studies is FA (Basser and Pierpaoli, 1996). Reductions in FA indicate differences in barriers to diffusion of water molecules. This may reflect altered white matter microstructure, which in turn could have functional significance in the mediation of hedonic responses to positive events (Keedwell et al., 2012).

Two studies have used diffusion MRI in order to specifically assess white matter microstructure of the MFB. One ROI-study demonstrated a trend towards reduced FA in the imMFB in currently depressed patients (Blood et al., 2010a). A recent diffusion MRI- based fibre tracking approach identified reduced FA in severely depressed melancholic MDD patients in segments of the slMFB connecting the VTA with the medial orbitofrontal cortex (OFC) and the dorsolateral prefrontal cortex (dlPFC) (Bracht et al., 2014). Lower FA was associated with more pronounced anhedonia and depression severity (Bracht et al., 2014). Moreover, diffusion MRI voxel-based (Liao et al., 2013; Zou et al., 2008), ROI (Bae et al., 2006; Blood et al., 2010a) and tract based spatial statistics (TBSS)(Korgaonkar et al., 2011; Zhu et al., 2011) studies have demonstrated reductions of FA in acute depression in the ALIC

and in prefrontal brain regions that likely incorporate segments of the slMFB (see Chapter 1).

However, it has not been determined whether white matter changes in these reward tracts are state-dependent or trait markers of vulnerability to depression. To date, no studies have examined if changes in FA in the MFB persist into remission.

While there is increasing evidence for white matter microstructure alterations during acute depression, less is known about white matter in remission (see Chapter 1). One tractography study found white matter microstructure alterations in fronto-limbic pathways in individuals with unmedicated remitted depression (RD) (Arnold et al., 2012). On the other hand, a ROI study found decreases of FA in the ventromedial prefrontal cortex, a region adjacent to the slMFB in treatment resistant depressed MDD but not in RD (de Diego-Adelino et al., 2013). One possible explanation for the absence of findings in RD is that remodeling of white matter microstructure occurs during remission. A one-year follow up longitudinal study in late life depression is consistent with this explanation (Taylor et al., 2011). Furthermore, FA of limbic pathways may differ between treatment responders and non-responders (Delorenzo et al., 2013; Taylor et al., 2008), which is also suggestive of white matter remodeling during recovery.

Based on previous work, the present study was designed to test the following hypotheses: Firstly, that FA would be reduced in the MFB in RD compared with ND individuals, consistent with the proposition that this represents a trait marker of MDD. Secondly, that, consistent with findings in acute MDD, FA in the slMFB tract would correlate positively with a measure of hedonic tone (or higher FA = lower anhedonia).

In accordance with previous approaches dividing tracts into subdivisions (Jones et al., 2013a) we reconstructed the two branches of the MFB (imMFB, slMFB) and analyzed them separately. As a methodological refinement of previous studies, we employed the damped Richardson Lucy algorithm (dRL) (Dell'acqua et al., 2010), which in contrast to DTI estimates multiple directions within a single voxel, and is therefore capable of improving the accuracy of tract reconstruction through regions of complex fibre architecture. Due to the particular importance of the VTA for the experience of pleasure (Nestler and Carlezon, 2006; Schultz et al., 1997), we included dorsal segments of the VTA projecting to the nucleus accumbens (NAcc)

and the prefrontal cortex (Bracht et al., 2014; Nieuwenhuys et al., 2008b). Second, we explored associations between hedonic tone and white matter microstructure of the imMFB and slMFB. To establish the specificity of potential findings we reconstructed the middle cerebellar peduncle (MCP) as a comparison tract (as we did not hypothesize, *a priori*, the MCP to be affected in RD). We also performed a whole brain group comparison of FA to complement the tract reconstruction approach.

2.3 Methods

2.3.1 Sample and measures

Eighteen RD, unmedicated women with a history of major depressive disorder (MDD) and 22 healthy controls without a history of MDD (ND, never depressed) were recruited from the staff and student body of the School of Psychology, Cardiff (recruitment was performed by Amie Doidge). Individuals were recruited from the same gender to reduce the potential effect of gender based variability of brain structure (Kanaan *et al*., 2014), thereby increasing the power to detect group differences. Females were specifically chosen because they have a higher incidence of depression than men, attributable to a greater incidence of first onset as opposed to chronicity or recurrence (Kessler *et al*., 1993). Controls were matched for age, gender and pre-morbid intelligence. Inclusion criteria for all participants were right-handedness and fluency in English. Exclusion criteria were contraindications for magnetic resonance imaging (MRI)-scans, a diagnosis of Axis I disorder, a current episode of depression, substance dependence and psychotropic medication. The Mini International Neuropsychiatric Inventory (MINI) (Sheehan *et al.*, 1998) was used to exclude a current episode of depression in all participants. Further, the MINI was used to confirm a history of a depressive episode in RD and the absence of a history of depression in ND. Results of the MINI were corroborated by a medical history. The MINI was also used to screen participants for a history of psychiatric disorders and drug or alcohol dependence. Additional questions were employed (regarding hospitalization, treatments, suicidal behaviour and psychosis) in order to rate RD participants on the Bipolar Affective Disorder Dimension Scale (BADDS) ï a dimensional scale for rating lifetime psychopathology in bipolar and unipolar disorders, taking in to account the number and severity of episodes (Craddock *et al.*, 2004). All participants completed the Beck Depression Inventory (BDI-II) (Beck *et al.*, 1996), the Fawcett Clark Pleasure Scale (FCPS) (Fawcett *et*

al., 1983) for assessment of hedonic tone and the National Adult Reading Test (NART) (Nelson and Willison, 1992), an assessment of pre-morbid intelligence. The cut-off score for moderate depression according to the BDI-II is 14. Higher scores on the FCPS indicate more pronounced capacity to derive pleasure. All questionnaires were completed in the presence of a psychologist who ensured that questionnaires were filled out correctly and to ensure that no misunderstandings occurred. All participants provided written informed consent. The study was approved by the School of Psychology Research Ethics committee.

2.3.2 Diffusion MRI scanning

Diffusion weighted MRI data were acquired on a 3T GE Signa HDx system (General Electric Healthcare) using a peripherally gated twice-refocused pulse-gradient spin-echo echo-planar imaging sequence providing whole oblique axial (parallel to the commissural plane) brain coverage. Data were acquired from 60 slices of 2.4 mm thickness, with a field of view 23 cm, and an acquisition matrix of 96 x 96 (yielding isotropic voxels of 2.4 x 2.4 x 2.4 mm, reconstructed to a resolution of 1.9 x 1.9 x 2.4 mm). Echo time (TE) was 87 ms and parallel imaging (ASSET factor = 2) was used. Diffusion encoding gradients (b = 1200 s/mm2) were applied along 60 isotropically-distributed directions (Jones *et al.*, 1999). Six additional non-diffusion weighted scans were collected. The acquisition time was approximately 26 minutes.

2.3.3 Structural MRI scanning

T1-weighted structural scans were acquired using an oblique-axial, 3D fast spoiled gradient recalled sequence (FSPGR) with the following parameters: Repetition time (TR)=7.9ms; TE=3.0 ms, inversion time=450ms, flip angle = 20º, 1mm isotropic resolution, with total acquisition time of approximately 7 minutes.

2.3.4 Diffusion MRI data pre-processing

The data were corrected for distortions and subject motion using an affine registration to the non-diffusion-weighted images, with appropriate re-orienting of the encoding vectors (Leemans and Jones, 2009). A single diffusion tensor model was fitted (Basser *et al.*, 1994) to the data in order to compute quantitative parameters

such as FA. The Damped Richardson-Lucy Algorithm (dRL) was used to estimate the fibre orientation density function (fODF) in each voxel (Dell'acqua *et al.*, 2010). Following the method of Pasternak et al. (Pasternak *et al.*, 2009; Metzler-Baddeley *et al.*, 2012), a correction for free water contamination of the diffusion tensor based estimates was applied.

2.3.5 Tractography

Deterministic tractography was performed using *ExploreDTI* Version 4.8.2 (Leemans *et al.*, 2009) following peaks in the fODF reconstructed from dRL (Dell'acqua *et al.*, 2010; Jeurissen *et al.*, 2013). For each voxel in the data set, streamlines were initiated along any peak in the fODF that exceeded an amplitude of 0.05. Thus (in contrast to DTI-based methods), multiple fibre pathways could be generated from any voxel. Each streamline continued in 0.5 mm steps following the peak in the ODF that subtended the smallest angle to the incoming trajectory. The termination criterion was an angle threshold > 45 degrees.

2.3.6 Tract reconstruction

The FA images of each subject were warped to their respective FSPGR image using the linear registration tool FLIRT (Jenkinson *et al.*, 2002). Inverse parameters were applied to transform the FSPGR image to the FA image. Afterwards, FSPGR images were used as a template to draw regions of interest (ROI) for virtual dissection of the different branches of the MFB. Seed regions were drawn by one experimenter (T.B.) who was blind to the diagnosis of participants. For both the imMFB and slMFB a ROI surrounding the VTA was drawn in the horizontal section. Anatomical borders were laterally the substantia nigra, anteriorly the mammillary bodies and posteriorly the red nucleus. For reconstruction of the imMFB a second ROI surrounding the hypothalamus was drawn on a horizontal section one section above the VTA ROI (see figure 2.1). For reconstruction of the slMFB a second ROI was drawn surrounding caudate and putamen on a coronal section at the height of the NAcc (see figure 2.2). The anatomical course of each tract was carefully checked for each subject. Due to the particular interest in the role of the MFB in reward processing, the focus was placed on segments of the MFB dorsal to the VTA including projections from the VTA to NAcc, hypothalamus and the OFC, core regions of reward processing (Haber and Knutson, 2010). Seed regions for the

comparison tract (MCP) were drawn on a coronal section, where left and right MCP can be clearly identified. The MCP was chosen because it can be reliably isolated but is not predicted *a priori* to be affected in RD. Because of the spatial overlap of left and right MCP in regions of the pontine nuclei (Nieuwenhuys *et al.*, 2008), the MCP was treated as a sole ROI. Mean-FA was derived for each reconstructed tract for each subject. In addition, the average MD and AD, RaD were computed, to facilitate follow up of any group differences seen in FA, our primary outcome measure.

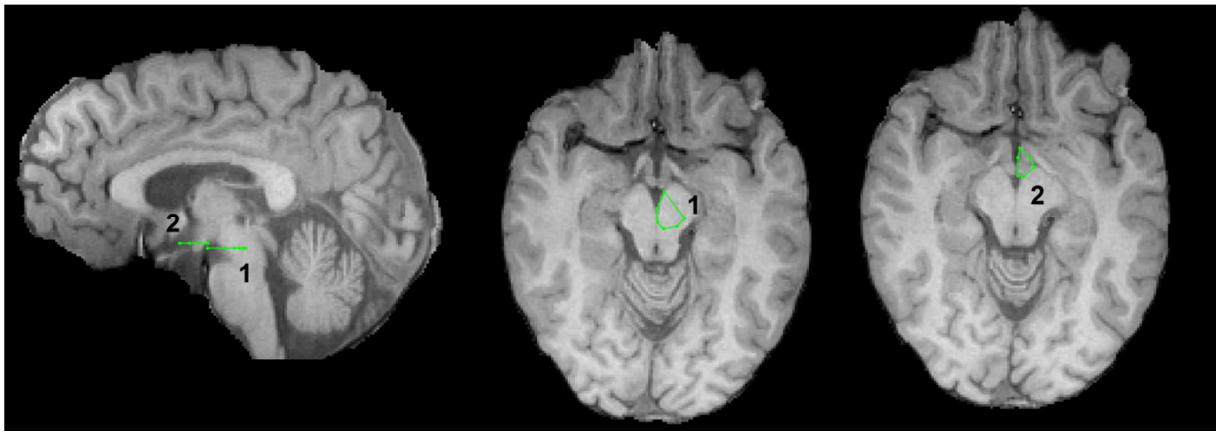

Figure 2.1 Seed regions for reconstruction of the imMFB

Seed regions (green) for the reconstruction of the infero-medial medial forebrain bundle (imMFB) are shown surrounding the ventral tegmental area (VTA (1)) and the hypothalamus (2).

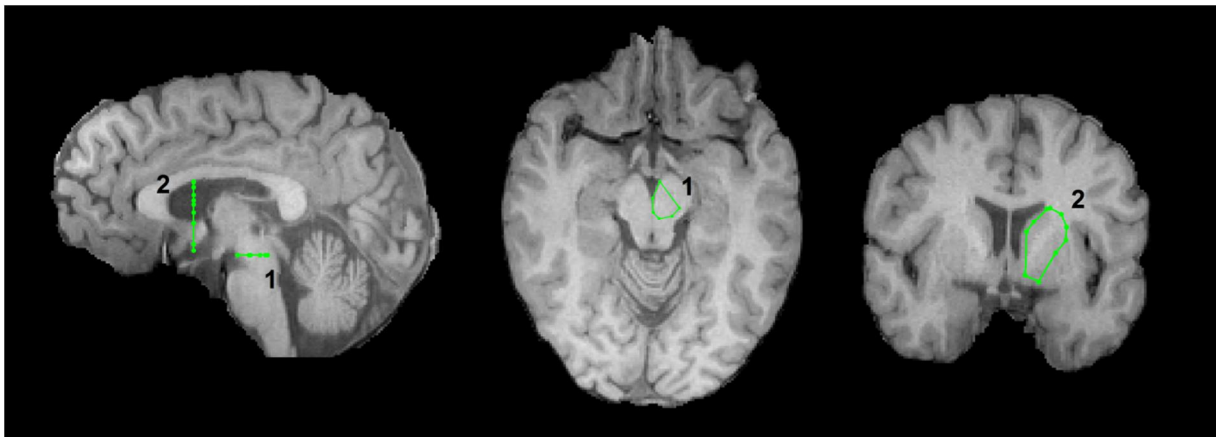

Figure 2.2 Seed regions for reconstruction of the slMFB

Seed regions (green) for the reconstruction of the supero-lateral medial forebrain bundle (slMFB) are shown surrounding the ventral tegmental area (VTA, (1)) and the anterior limb of the internal capsule at the height of the nucleus accumbens (NAcc (2)).

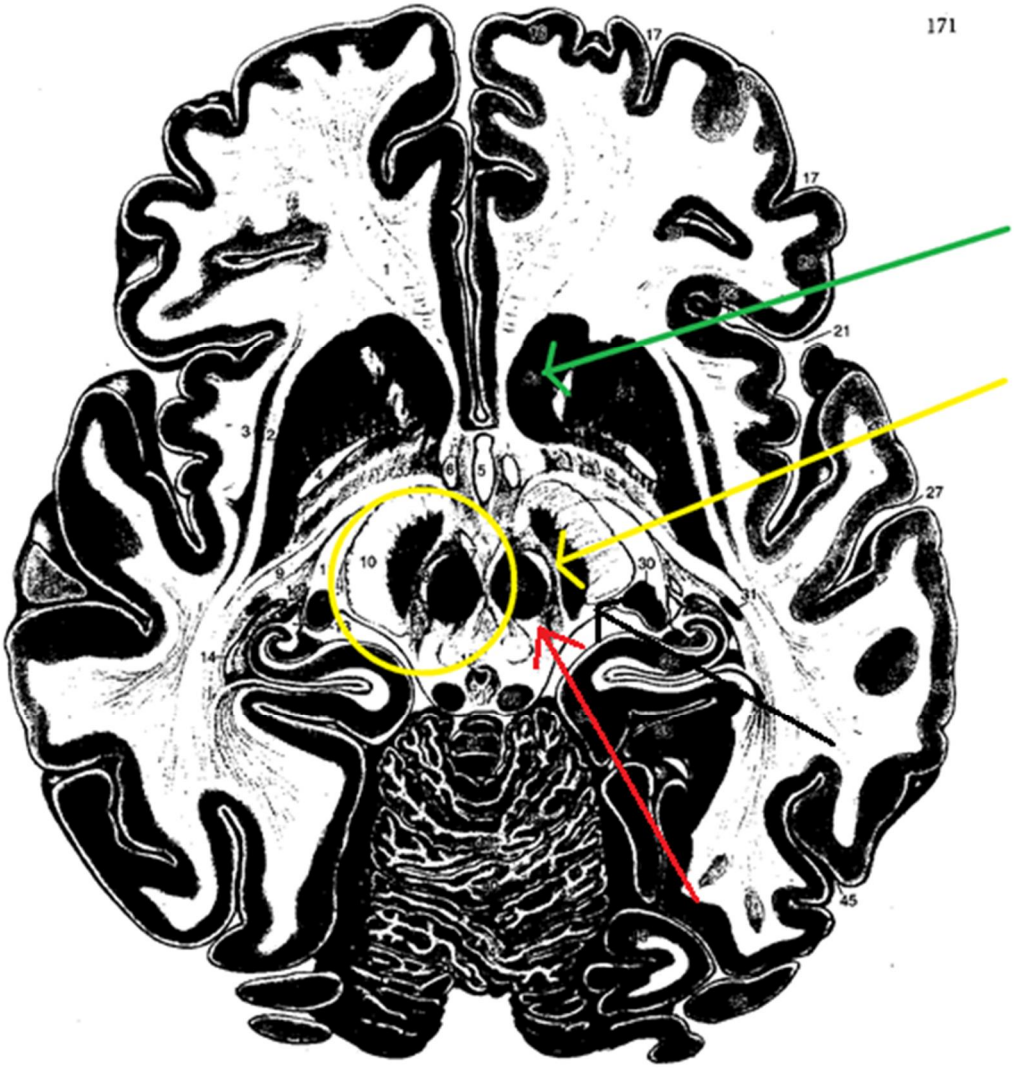

Figure 2.3 Anatomical borders of the medial forebrain bundle

The medial forebrain bundle (yellow arrow, 8) and its anatomical borders are illustrated based on a modified picture from (Nieuwenhuys *et al.*, 2008). The medial forebrain bundle ist located laterally and anterior of the red nucleus (red arrow) and medially of the substantia niga (black arrow). The nucleus accumbens is a medial expansion of the the head of the caudate nucleus (green arrow).

2.3.7 Statistical analysis

Statistical analyses were performed using SPSS (SPSS, Inc., Chicago, Illinois). A MANCOVA was used to explore main effects of group (ND versus ND) and hedonic tone (FCPS-score), and their interactions on mean-FA of the four respective tracts. To follow up any significant main effects of group, hedonic tone or group x hedonic tone interactions, four separate ANCOVAs were calculated (one ANCOVA for each tract, fixed factor group (ND, RD), covariate hedonic tone). The critical p-value threshold was adjusted using a Bonferroni correction for multiple comparisons (p =

0.05 / 4 = 0.0125). Where significant effects on mean FA were found, the effects on additional metrics (MD, RaD, and AD) were explored.

2.3.8 Whole brain Voxel-Wise Analysis

Voxel-wise statistical analysis of FA data was carried out using FSL tract based spatial statistics (TBSS) software (Smith *et al.*, 2004; Smith *et al.*, 2006). FA data were projected onto a mean FA tract skeleton, before applying voxelwise cross-subjects statistics. The tract skeleton was thinned using an FA threshold > 0.2. Group comparisons between RD and ND of FA on this fibre skeleton were then performed using threshold free cluster-enhancement (TFCE). Group comparisons were deemed to be significant at a cluster threshold of $p < 0.05$. Correlations between FCPS score and FA across the skeleton were also examined.

2.4 Results

2.4.1 Sample characteristics

Groups did not differ regarding age, gender, pre-morbid intelligence, hedonic tone (FCPS score) or handedness. None of the participants met criteria for MDD according to the Mini International Neuropsychiatric Interview. RD patients had significantly higher BDI scores (for details see Table 2.1).

Our participants had a mean score of 65 ± 10 on the BADDS, indicating a moderate to severe history of depression. Seven RD had a history of treatment with antidepressive medication, while eleven were medication-naïve, and four had a history of treatment with psychotherapy. None had a history of psychotic depression or had been hospitalized for treatment. Fifteen patients had a history of depressive episodes that met DSM-IV criteria for melancholic depression, as defined by the MINI and four had a history of a suicide attempt.

	RD (n = 18)	ND (n = 22)	P
Age	22.4 ± 3.6	22.5 ± 4.5	0.933
Female gender (%)	100	100	
Right Handedness (%)	100	100	
Premorbid Intelligence	113 ± 5	112 ± 5	0.647
Fawcett score	120 ± 11	122 ± 11	0.687
BDI score	11.4 ± 10.4	2.7 ± 4	0.001*
Number of episodes	2.22 ± 3.6	0	<0.001*

Table 2.1 Demographics

Demographics are shown for remitted depressed (RD) and never depressed (ND) participants. Abbreviations: RD, remitted depressed; ND never depressed; BDI, Beck-Depression-Inventory. Significant at $p < 0.05$.

2.4.2 Tract specific measurements

The MANCOVA revealed a main effect of hedonic tone (FCPS-score) on mean-FA across the four tracts ($F(4, 33) = 4.112$, $p = 0.008$), but no main effect of group ($F(4, 33) = 0.522$, $p = 0.720$) or significant group x hedonic tone interaction ($F(4, 33) = 0.454$, $p = 0.769$). This main effect was followed up using four separate ANCOVAs. There was only a significant main effect of hedonic tone on mean-FA for the left slMFB ($F(1, 36) = 10.712$, $p = 0.002$), but not for left imMFB ($F(1, 36) = 1.812$, $p = 0.185$), right imMFB ($F(1, 36) = 2.501$, $p = 0.344$) or right slMFB ($F(1, 36) = 0.920$, $p = 0.344$).

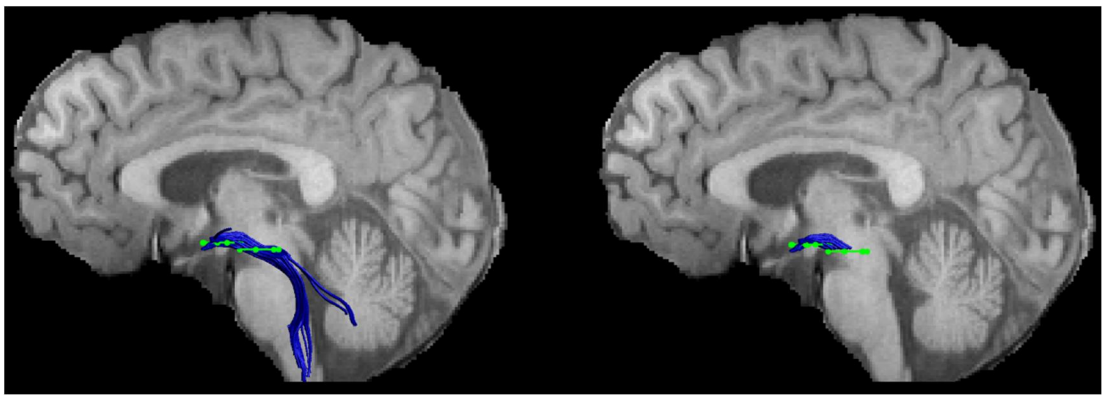

Figure 2.4 Reconstruction pipeline of the imMFB

The reconstruction pipeline of the reconstruction of the infero-medial medial forebrain bundle (imMFB) is shown before (left side) and after (right side) using the splitter tool to extract segments of the imMFB being localized dorsal of the ventral tegmental area (VTA).

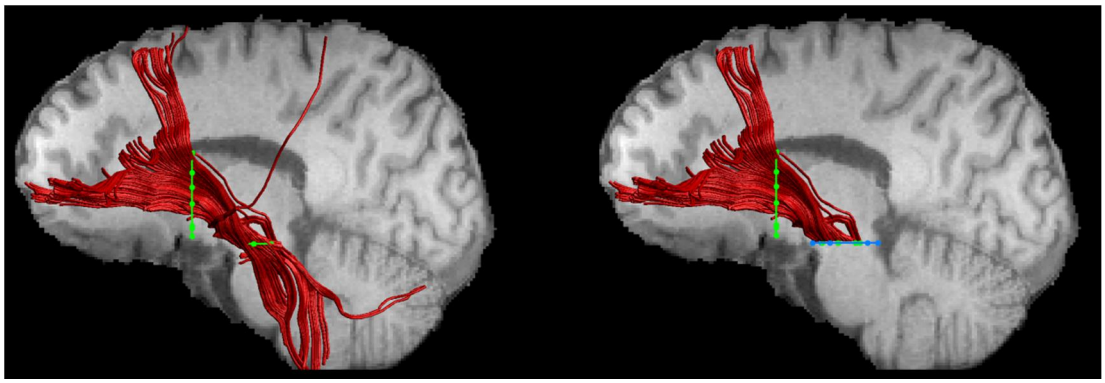

Figure 2.5 Reconstruction pipeline of the slMFB

The reconstruction pipeline of the reconstruction of the infero-medial medial forebrain bundle (imMFB) is shown before (left side) and after (right side) using the splitter tool to extract segments of the imMFB being localized dorsal of the ventral tegmental area (VTA).

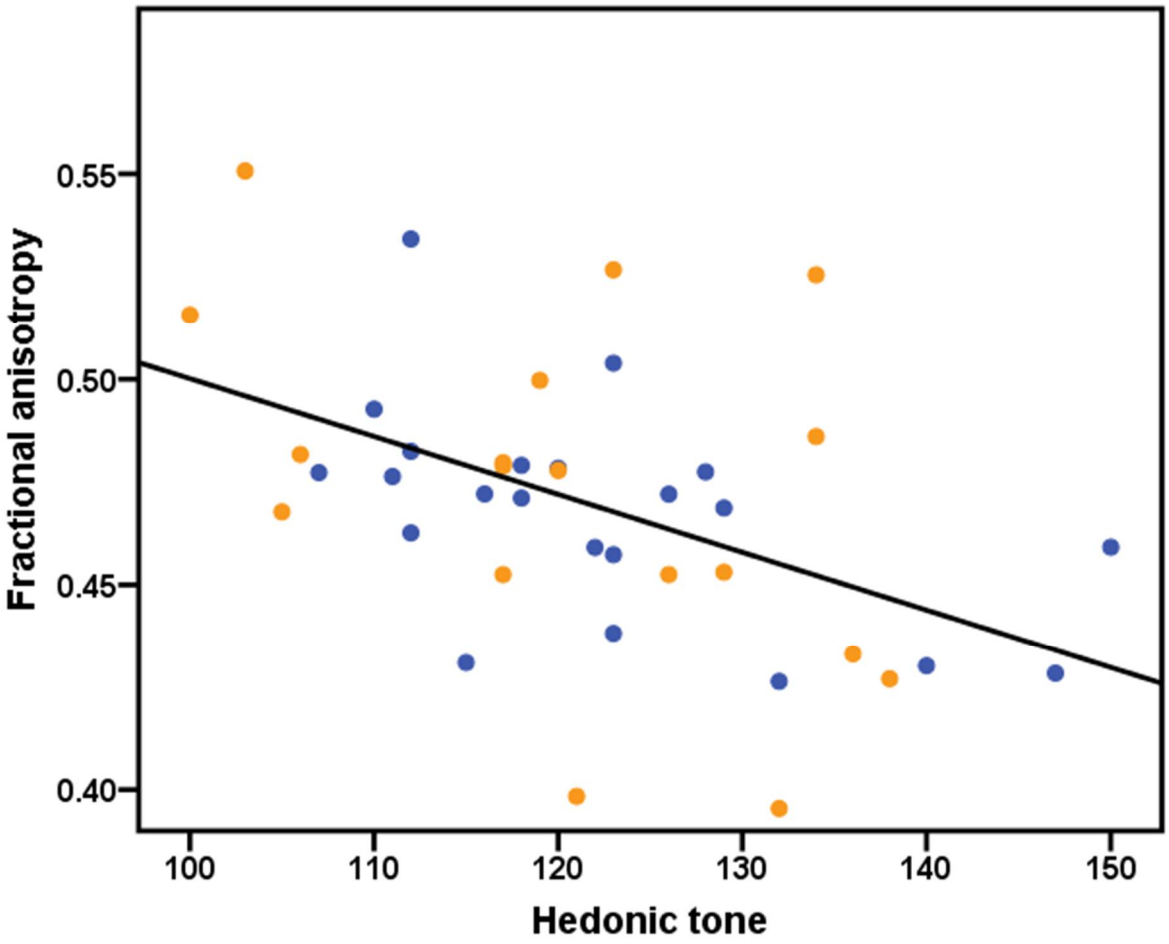

Figure 2.6 Correlation between FA and hedonic tone

The negative correlation across the whole sample between fractional anisotropy (FA) of the left supero-lateral medial forebrain bundle (slMFB) and hedonic tone is displayed (never depressed, ND blue; remitted depressed, RD orange).

In accordance with these findings there was a sole negative correlation between FCPS-scores and mean-FA of the left slMFB ($r = -0.48$, $p = 0.002$) across all individuals (Figure 2), explaining 20.6% of the variance. FA of right slMFB ($r = -0.146$, $p = 0.369$), left imMFB ($r = -0.232$, $p = 0.150$) and right imMFB ($r = -0.247$, $p = 0.125$) did not correlate with FCPS scores. Mean-FA of none of the tracts correlated with BDI-scores.

Secondary correlational analyses with diffusion properties demonstrated that the negative correlation between FCPS scores and FA mainly reflected changes in RaD (RaD: $r = 0.460$, $p = 0.003$; MD: $r = 0.337$, $p = 0.033$; AD: $r = -0.281$, $p = 0.079$).

FA in the comparison tract (MCP) did not differ between groups (mean-FA RD = 0.46 ± 0.03, mean-FA ND= 0.47 ± 0.03, $T = 1.215$, $df = 38$, $p = 0.236$). There was no significant correlation between FCPS and MCP FA ($r = -0.32$, $p = 0.842$).

2.4.3 Voxel-Wise whole brain analysis

For the TBSS results there were no significant group differences in FA and no significant correlations between FCPS scores and FA in any brain region.

2.5 Discussion

Our study has two main findings. First, we found no differences in FA for any MFB region between unmedicated RD and ND individuals, suggesting that microstructural abnormalities of the MFB are not present in individuals with remitted depression. Second, we have demonstrated a negative correlation between the capacity to derive pleasure and mean-FA of the left slMFB in all individuals, irrespective of depression history. Mean-FA explained 21% of the variance of hedonic tone. Decreases of FA were mainly driven by decreases of RaD. Hedonic tone did not correlate with FA in the control tract or the imMFB.

The absence of group differences in FA in our study leads us to reject our first hypothesis. However, this complements findings of reduced FA of the slMFB in severely melancholic but not in moderately depressed patients (Bracht *et al.*, 2014). Alike, in another study whole brain FA reductions were observed in chronic treatment resistant patients but not in remitted, unmedicated patients (de Diego-

Adelino *et al.*, 2013). Therefore, whilst previous research points to white matter microstructure alterations of the slMFB in severely depressed patients (Bracht *et al.*, 2014), to date there is no evidence for altered structural connectivity in remission.

Collectively, these results suggest that reductions in FA in the MFB are state-dependent effects and not trait markers of vulnerability, and only appear in melancholic depression. It follows that neuroplastic changes could occur upon recovery, reversing changes observed during the acute illness. White matter microstructure may change even within very short time scales (Sagi *et al.*, 2012), including after moderate interventions such as learning how to juggle (Scholz *et al.*, 2009) or half an hour of aerobic exercise per day (Erickson *et al.*, 2011). Consistent with this explanation a one-year follow up longitudinal study in late life depression demonstrated normalization of FA in other white matter tracts upon recovery (Taylor *et al.*, 2011). Furthermore, FA of limbic pathways may differ between treatment responders and non-responders (Taylor *et al.*, 2008; Delorenzo *et al.*, 2013), which is also suggestive of white matter remodeling during recovery. Longitudinal studies of changes in MFB FA in response to treatment are indicated to further explore the neuroplasticity of these tracts in relation to recovery.

A further explanation is that, while some of the RD individuals in this study might go on to develop a more severe or treatment resistant course, any abnormalities of white matter microstructure in this group could be masked by those RD individuals with a putatively better prognosis. Longitudinal studies would also inform this research question.

Our results suggest that lower FA in the left slMFB is associated with more pronounced capacity to derive pleasure in RD and ND. Hence, the correlation is in the opposite direction to that hypothesized, and previously demonstrated in acute depression, where slMFB FA correlated negatively with anhedonia scores (Bracht *et al.*, 2014).

However, different microstructural changes could be occurring in the different populations while still having similar effects on hedonic processing. For example, greater myelination and larger axonal diameter both increase conduction velocity in a tract but have opposite effects on FA, all other factors being constant. Therefore, changes in FA alone cannot define any particular change in ñfibre integrityò(Jones *et al.*, 2013b). Novel white matter mapping techniques such as the composite hindered and restricted model of diffusion (CHARMED) (De Santis *et al.*, 2013) or

multicomponent driven equilibrium pulse observation of T1 and T2 (McDESPOT) (Deoni *et al.*, 2005) provide sub-compartment specific measures (e.g. on axonal diameter or myelination) and could lead to a better understanding of the neurobiological underpinnings of these findings.

The associations identified between individual differences in the white matter microstructure of the slMFB and the capacity to derive pleasure are indirectly supported by animal research and by fMRI and PET studies in humans. Research in animals convincingly demonstrates a key role of the VTA, NAcc and OFC in reward processing (Schultz *et al.*, 1997; Haber and Knutson, 2010). Furthermore, fMRI and PET studies in humans demonstrate activations of NAcc, VTA and OFC when perceiving pleasure (Drevets *et al.*, 2001; Kringelbach, 2005). Individuals with more pronounced hedonic responses experience relatively greater activations in these areas to the same pleasurable stimulus (Breiter *et al.*, 1997; Blood and Zatorre, 2001; O'Doherty *et al.*, 2001). This also appears to be true in depression, although the evidence in MDD is less consistent (Keedwell *et al.*, 2005; Smoski *et al.*, 2009; Zhang *et al.*, 2013). The slMFB structurally connects these core regions of the reward system (Nieuwenhuys *et al.*, 2008), and may therefore play an essential role in integrating information leading to the perception of pleasure. Therefore, our finding of an association between hedonic tone and microstructure of the slMFB is consistent with this body of literature. However, one obvious caveat is that our study design does not allow us to establish the direction of causality.

MFB microstructure could mediate individual differences in both subclinical (trait) anhedonia, as in this study, and clinical (depressive) anhedonia. The central importance of MFB function in depression is supported by Deep Brain Stimulation (DBS) research: DBS targeting the ventral striatum/MFB provides some relief of depression in a subset of treatment resistant patients (Malone *et al.*, 2009; Bewernick *et al.*, 2010; Schlaepfer *et al.*, 2013).

The lack of any significant findings for our TBSS analyses is consistent with increasing evidence (Kanaan *et al.*, 2006; Keedwell *et al.*, 2012) that tract averaging approaches are more sensitive than voxel-based approaches; possibly because subtle microstructural differences only reach significance if averaged over the whole tract, but not if compared on a voxel by voxel basis.

This study has some limitations. First, although none of the RD met criteria for diagnoses of a current episode for depression, groups differed with regard to depressive symptomatology. However, scores on the BDI-II did not correlate with FA of imMFB and slMFB which though may be as a result of small variance in BDI-scores. Also, groups did not differ regarding hedonic tone, and there was no group x hedonic tone interaction. Second, our young sample, who remained well while unmedicated, with relatively few previous episodes, may not be representative of the majority of patients with MDD seen in clinical practice. However, including medicated individuals would have made any results difficult to interpret. Future studies could include older patients, while attempting to control for the independent effect of age on white matter microstructure per se. Third, since we aimed to investigate remitted, fully recovered participants our participants did not receive ongoing treatment. Therefore we did not have access to clinical files for validation of previous diagnoses. Fourth, we did not have information on the menstrual cycle of participants which may influence white matter microstructure (De Bondt *et al.*, 2013).

In summary, we linked the capacity to derive pleasure to white matter microstructure of specific sub-compartments of the MFB. We found a negative association between hedonic tone and mean-FA of the slMFB in a non-clinical group. Our findings corroborate the important role of the slMFB in reward processing and its potential role in depression. Longitudinal studies are needed to assess the prognostic value of slMFB microstructure in MDD, and to investigate if white matter changes occur in tandem with clinical recovery. Finally, advanced white matter mapping techniques such as CHARMED (De Santis *et al.*, 2013) or McDESPOT (Deoni *et al.*, 2005) provide promise in clarifying the microstructural changes that underlie changes in FA.

3 Limbic White Matter Microstructure Plasticity Reflects Recovery from Depression

The work presented in this chapter has been published:

Bracht, T., Jones, D.K., Muller, T.J., Wiest, R., Walther, S., 2015. Limbic white matter microstructure plasticity reflects recovery from depression. Journal of affective disorders 170, 143-149.

The published article has been edited for this chapter in order to include additional results and to avoid repetition across Chapters 1 and 2. However, this chapter partly covers background information already dealt with in the previous chapters.

I acknowledge Oliver Höfle for recruitment, testing and scanning of participants.

3.1 Summary

White matter microstructure alterations of limbic and reward pathways have been reported repeatedly for depressive episodes in major depressive disorder (MDD) and bipolar disorder (BD). However, findings during remission are equivocal. It was the aim of this study to investigate if white matter microstructure changes during the time course of clinical remission. Fifteen depressed patients (11 MDD, 4 BD) underwent diffusion-weighted MRI both during depression, and during remission following successful antidepressive treatment (average time interval between scans = 6 months). Fractional anisotropy (FA) was sampled along reconstructions of the supero-lateral medial forebrain bundle (slMFB), the cingulum bundle (CB), the uncinate fasciculus (UF), the parahippocampal cingulum (PHC) and the fornix. Repeated measures ANCOVAs controlling for the effect of age were calculated for each tract. There was a significant main effect of time (inter-scan interval) for mean-FA for the right CB and for the left PHC. For both pathways there was a significant time x age interaction. In the right CB, FA increased in younger patients, while FA decreased in older patients. In the left PHC, a reverse pattern was seen. FA changes in the right CB correlated positively with symptom reductions. Mean-FA of UF, slMFB and fornix did not change between the two time points. In conclusion right CB and left PHC undergo age-dependent plastic changes during the course of remission and may serve as a state marker in depression. UF, slMFB and FO microstructure remains stable.

3.2 Introduction

Alterations of white matter pathways connecting important brain regions of the limbic and the reward system may be associated with major depressive disorder (MDD)(Aghajani et al., 2013; Blood et al., 2010a; Bracht et al., 2014; de Diego-Adelino et al., 2013). Diffusion weighted magnetic resonance imaging (DW-MRI) enables white matter microstructure of the brain to be quantified non-invasively (Basser et al., 1994). DW-MRI-based indices such as FA characterize the extent to which water molecules are hindered by the tissue microstructure (Basser and Pierpaoli, 1996) and are commonly used for an *in vivo* assessment of microstructural changes in depressive disorders (Liao et al., 2013; Sexton et al., 2009).

Previous publications reported DW-MRI based alterations of limbic and reward pathways in MDD during depressive episodes (for review and meta-analyses see (Liao et al., 2013; Sexton et al., 2009)). For instance, both increases (Aghajani et al., 2013) and decreases (Zhang et al., 2012) of FA were found in the UF during depression. Further, FA reductions in the slMFB in melancholic depression were associated with depression severity and anhedonia (Bracht et al., 2014).

In contrast, there is much less evidence for white matter microstructural alterations in remitted depression (de Diego-Adelino et al., 2013). Whilst some studies have reported differences in fronto-limbic pathways in remitted MDD and remitted bipolar disorder (BD) (Arnold et al., 2012; Houenou et al., 2007), we (Chapter 2) and others did not detect any group differences between remitted MDD and healthy controls (de Diego-Adelino et al., 2013). Given that depression is an episodic disorder with remitting-relapsing course, these findings lead to the question whether remission is accompanied by neuroplastic changes. Indirect evidence in support of neuroplasticity comes from findings that FA predicts treatment response (Delorenzo et al., 2013; Hoogenboom et al., 2014; Taylor et al., 2008). Longitudinal studies enable this question to be addressed directly. Previous research both in humans and animals strongly supports the hypothesis that white matter microstructure is highly plastic (Blumenfeld-Katzir et al., 2011; Sagi et al., 2012; Scholz et al., 2009). Changes of white matter microstructure could be demonstrated following moderate interventions such as learning to juggle (Scholz et al., 2009) or training on a spatial navigation task (Sagi et al., 2012). One longitudinal study in old age depression found FA changes in the cingulum bundle (CB) in remitters but not in non-remitters (Taylor et al., 2011).

It was the aim of this study to investigate if white matter microstructure of important pathways of the limbic and the reward system changes during the course of remission. Therefore, patients with a diagnosis of MDD or BD underwent diffusion MRI scans during depressive episodes and were scanned again when being remitted. We investigated the slMFB, CB, UF, parahippocampal cingulum (PHC) and the fornix. In all of these pathways white matter microstructure alterations have been reported during depressive episodes (Aghajani et al., 2013; Bracht et al., 2014; Charlton et al., 2013; Kieseppa et al., 2010; Korgaonkar et al., 2011; Zhang et al., 2012; Zhu et al., 2011). White matter microstructure of the slMFB and the CB may be related to hedonic tone and to anhedonia in depression (Bracht et al., 2015a; Bracht et al., 2014; Coenen et al., 2012; Keedwell et al., 2012; Schlaepfer et al.,

2013b), while the UF microstructure may mediate impaired emotion regulation in depression (Aghajani et al., 2013; Zhang et al., 2012). Hippocampal pathways (fornix and PHC) play a core role for reward processing (Haber and Knutson, 2010). In addition, the hippocampus is the only region in the human brain with evidence for neurogenesis, and therefore of particular importance when investigating neuroplasticity (Rakic, 2002). We hypothesized that plastic changes of white matter microstructure in these pathways occur during the longitudinal course of remission. In keeping with previous reports, we chose mean-FA of these tracts as the primary outcome measure.

3.3 Methods

A total of 15 (11 MDD, 4 BD) patients were recruited from the inpatient department of the University Hospital of Psychiatry, Bern, Switzerland (recruitment has been performed by Oliver Höfle). Diagnoses were given according to DSM-IV by experienced psychiatrists using clinical interviews, rating scales and review of all case files. The structured clinical interview for DSM-IV part II (SCID-II) was used to exclude co-morbid personality disorders. Further exclusion criteria were a history of significant head trauma, electroconvulsive therapy, substance abuse or dependence other than nicotine. If meeting criteria for a depressive episode, the first MRI scan was performed (see below). Further clinical assessments were performed every four weeks. When criteria for remission were met (as defined by a Hamilton Depression Rating Scale (HAMD) (Beck et al., 1961; Hamilton, 1967) < 8 and Beck Depression Inventory (BDI) < 10), the second MRI scan was performed. Following the two respective MRI-scans physical activity of participants was assessed using 24-hour actigraphy (details of actigraphy recordings are described in Chapter 4 which explicitly focuses on the white matter correlates of motor activity). Detailed demographics of our sample are given in Table 3.1. Data derived from the first MRI scan of MDD patients were used for group comparisons with healthy controls from previous studies that used an identical acquisition protocol (Bracht et al., 2012a; Bracht et al., 2014; Walther et al., 2012b). The study was approved by the local ethics committee (KEK-BE 196/09) and in accordance with the Declaration of Helsinki. All participants provided informed written consent.

	Depressed	Remitted	Analyses
Number of episodes	6.6 ± 6.2		
Duration of illness (years)	6.9 ± 6.5		
Duration of current episode (months)	4.9 ± 5.2		
Duration between scans (months)	6.1 ± 2.7		
BDI	26 ± 9	6 ± 5	P < 0.001*
HAMD	24 ± 5	5 ± 4	P < 0.001*
MADRS	24 ± 4	4 ± 4	P < 0.001*
Antidepressants			
SSRI	2	4	
Venlafaxine	1	3	
Mirtazapine	5	2	
Venlafaxine and Mirtazapine	3	2	
TCA	4	6	
Lithium	2	4	
Mianserin	0	1	
Atypical antipsychotics	9	6	
Zolpidem	7	1	
Age (years)	45 ± 12		
Gender (women %)	66.7%		
Duration of education (years)	13.7 ± 2.6		
Activity level (counts/ day)	12944 ± 4623	19726 ± 7804	P=0.015*
Smokers (%)	33		

Table 3.1 Demographics

Abbreviations: BDI, Beck Depression Inventory; HAMD, Hamilton Depression Rating Scale; Montgomery-Asberg Depression Rating Scale; SSRI, Selective Serotonin Reuptake Inhibitor; TCA, Tricyclic Antidepressants

3.3.1 Structural MRI scanning

All data were acquired on a 3T Siemens MR scanner (Siemens Magnetom Trio, Erlangen, Germany, 12-channel head coil). High-resolution T1-weighted data were obtained with the MDEFT sequence (Deichmann et al., 2004), with parameters as follows: 176 sagittal slices, 256 × 224 matrix , isotropic resolution of 1 mm^3, TR/TE = 7.92 ms/2.48ms, 16° flip angle, inversion time 910 ms, and fat saturation (total acquisition time = 12 minutes). Identical prescription of MR images was achieved using the Siemens Autoalign sequence, which automatically sets up consistent slice orientation based on a standard MRI atlas.

3.3.2 Diffusion MRI scanning

For diffusion MRI measurements, we used a spin-echo EPI sequence (55 slices, FOV = 256 × 256 mm^2, sampled on a 128 × 128 matrix resulting in 2 mm^3 voxel size, TR/TE = 6000/78 ms) covering the whole brain (40 mT/m gradient, 5/8 partial Fourier, no acceleration factor). Diffusion-weighted images were positioned in the axial plane parallel to the AC-PC line and measured along 42 directions with a b-value = 1300 s/mm^2. The sequence included four B0 images without diffusion weighting (the first and every subsequent 12^{th} image). We used a balanced and rotationally invariant diffusion-encoding scheme over the unit sphere to generate the DTI data (Hasan et al., 2001).

3.3.3 Diffusion MRI data pre-processing

Data analyses was performed using *ExploreDTI* (Leemans et al., 2009b). The data were corrected for distortions and subject motion using an affine registration to the non-diffusion-weighted images, with appropriate re-orienting of the encoding vectors (Leemans and Jones, 2009). Further, an echo planar imaging (EPI) correction was performed warping the diffusion images to the MDEFT images resulting in a 1x1x1 mm resolution for further processing. A single diffusion tensor model was fitted (Basser et al., 1994) to the diffusion data in order to compute quantitative parameters such as FA. Following the method of Pasternak et al. (Pasternak *et al.*, 2009; Metzler-Baddeley *et al.*, 2012), a correction for free water contamination of the diffusion tensor based estimates was applied.

3.3.4 Tractography

Whole brain tractography was performed using an algorithm similar to that described by (Basser et al., 1994). Termination criteria were an angle threshold > 45 degrees and FA < 0.2. Tracts were reconstructed using anatomically defined regions of interest (ROI). The slMFB has been reconstructed as described in detail in Chapter 2. One horizontal ROI was placed surrounding the ventral tegmental area (VTA). Anatomical borders were laterally the substantia nigra, anteriorly the mammillary bodies and posteriorly the red nucleus (Nieuwenhuys et al., 2008b). A second ROI was drawn surrounding caudate and putamen on a coronal section at the height of the nucleus accumbens (NAcc). Due to the particular interest in the role of the MFB in reward processing, the focus was placed on segments of the MFB dorsal to the VTA including projections from the VTA to NAcc, hypothalamus and the OFC, core

regions of reward processing. For reconstruction of the UF two coronal ROIs were placed approximately at the height of the NAcc surrounding the emerging temporal lobe and the region lateral to caudate and putamen. The CB and the PHC have been reconstructed according to (Jones et al., 2013a). For the CB two coronal ROIs were placed five slices anterior and five slices posterior to the rostro-caudal midpoint of the body of the corpus callosum (Jones et al., 2013a). For reconstruction of the PHC one horizontal ROI was placed at the height of the most ventral point of the splenium, and a second ROI was place four slices above (Jones et al., 2013a). For reconstruction of the fornix a coronal ROI was placed around the columns of the fornix (Metzler-Baddeley et al., 2013). Seed regions are visualized in figure 3.1, resulting tracts in figure 3.2. For reconstruction of the slMFB please refer to Chapter 2. The anatomical course of each tract was carefully checked for each subject, and mean-FA was derived for each reconstructed tract. In addition, the average MD, AD and RaD were computed, to facilitate follow up of any group differences seen in FA, our primary outcome measure.

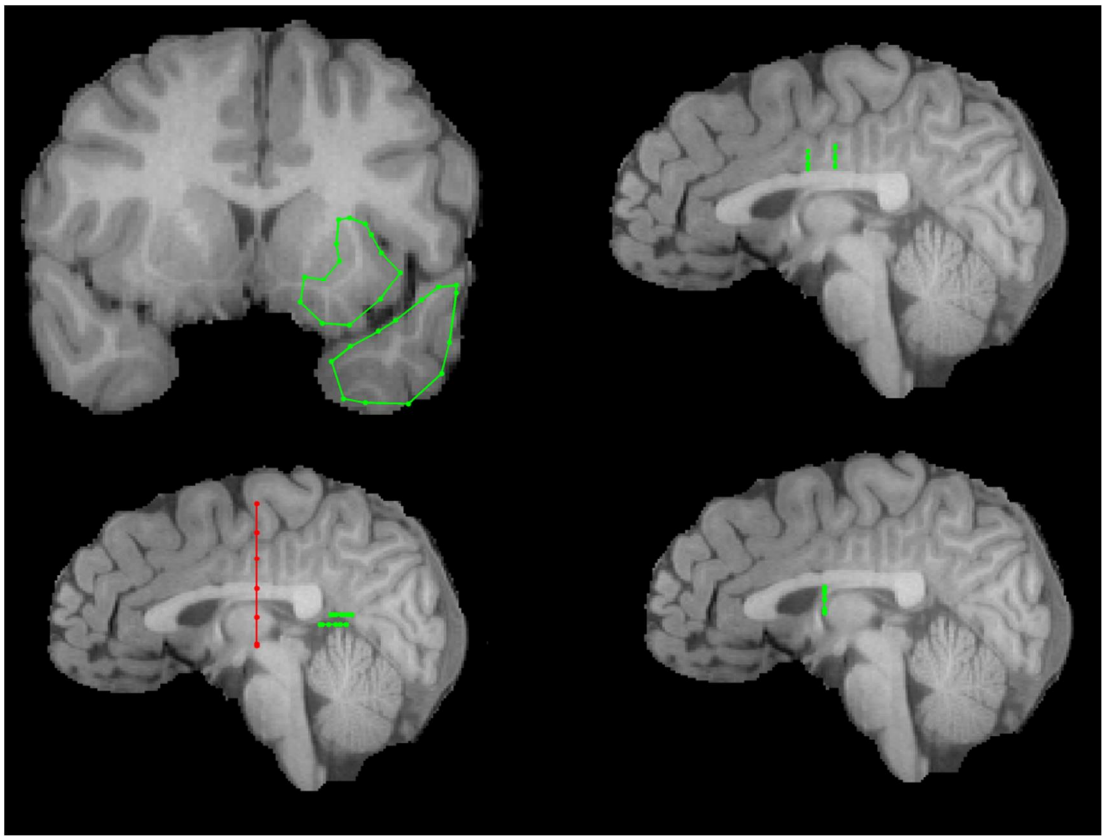

Figure 3.1 Visualization of seed regions of the UF, CB, PHC and fornix

Seed regions (green) and NOT-gates (red) of the uncinate fasciculus (UF), cingulum bundle (CB), parahippocampal cingulum (PHC) and the fornix are shown from left to right and top to bottom.

3.3.5 Statistical analysis

Statistical analyses were performed using SPSS (SPSS, Inc., Chicago, Illinois). Repeated measures ANCOVAs controlling for the effect of age have been calculated for each of the four bilateral tracts (slMFB, UF, CB, PHC) and the fornix. Age was entered as a covariate. The p-value was adjusted using a Bonferroni correction for multiple comparisons resulting in a level of significance of $p < 0.0056$ ($0.05 / 9 = 0.0056$).

Where significant effects on mean FA were found, analyses of the effects on additional metrics (MD, RaD, and AD) were explored. Further, where significant FA changes were found, we calculated correlations between the percentage of the absolute change of FA and reductions in HAMD overall depression scale ratings scores. We expected that more pronounced clinical improvements would be associated with more marked FA changes.

3.4 Results

There was a significant main effect of time (inter-scan interval, 1st MRI scan during depression, 2nd MRI-scan during remission) for mean-FA for the right CB and for the left PHC (see Table 3.2). Main effects of age were not significant for any of the tracts. For both pathways with significant main effect of time (right CB and left PHC) there was a significant time x age interaction. This interaction was reflected by a pattern of both increases and decreases in FA that depended on age, and also on the tract in which the measurements were made (see Figure 3.3).

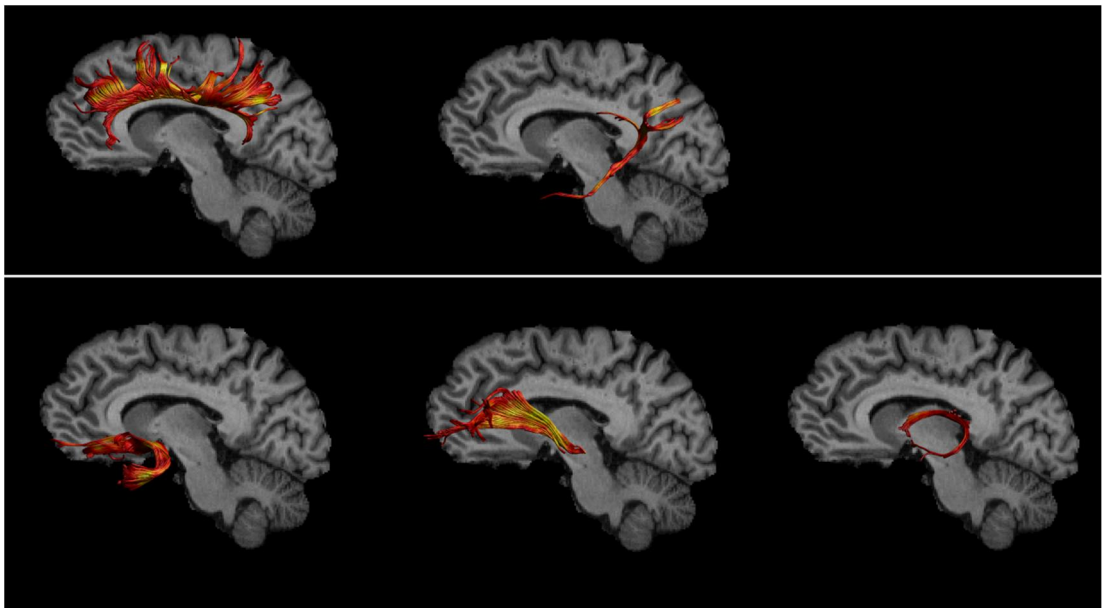

Figure 3.2 Typical reconstructions of CB, PHC, UF and fornix

Reconstructed fibre tracts are displayed for an individual subject. In the first row fibre tracts with significant fractional anisotropy (FA)-changes during remission are displayed (from left to right cingulum bundle, parahippocampal cingulum). In the second row fibre tracts with no significant FA-changes during remission are shown (from left to right uncinate fasciculus, supero-lateral medial forebrain bundle and fornix). Images are overlaid on a structural (T1-weighted) image. FA-metrics are superimposed on the reconstructed pathways.

Main effect time	**Main effect age**	**Time x Age**
Supero-lateral medial forebrain bundle (left)		
F(1,13) = 0.007, p = 0.935	F(1,13) = 1.515, p = 0.240	F(1,13) = 1.628, p = 0.224
Supero-lateral medial forebrain bundle (right)		
F(1,13) = 0.925, p = 0.354	F(1,13) = 0.004, p = 0.952	F(1,13) = 1.202, p = 0.293
Cingulum bundle (left)		
F(1,13) = 0.001, p = 0.980	F(1,13) = 0.237, p = 0.635	F(1,13) = 0.030, p = 0.866
Cingulum bundle (right)		
F(1,13) = 12.092, p = 0.004*	F(1,13) = 0.775, p = 0.395	F(1,13) = 14.222, p = 0.002*
Uncinate fasciculus (left)		
F(1,13) = 0.896, p = 0.361	F(1,13) = 0.686, p = 0.422	F(1,13) = 1.628, p = 0.224
Uncinate fasciculus (right)		
F(1,13) = 0.046, p = 0.834	F(1,13) = 0.372, p = 0.553	F(1,13) < 0.001, p = 0.993
Parahippocampal cingulum (left)		
F(1,13) = 13.828, p =	F(1,13) = 2.148, p = 0.166	F(1,13) = 10.078, p =

0.003*		0.007*
Parahippocampal cingulum (right)		
F (1,13) = 1.871, p = 0.195	F(1,13) = 3.037, p = 0.105	F(1,13) = 2.049, p = 0.176
Fornix		
F(1,13) = 0.734, p = 0.407	F(1,13) = 5.234, p = 0.040	F(1,13) = 1.061, p = 0.322

Table 3.2 Repeated measures ANCOVAs for fractional anisotropy

There was a positive correlation of age and relative FA-changes (FA-remitted (2nd MRI scan) divided by FA-depressed (1st MRI scan)) for the left PHC (r = 0.671, p = 0.006) and a negative correlation of age and relative FA-changes for the right CB (r = -0.737, p = 0.002) (see Figure 3.2).

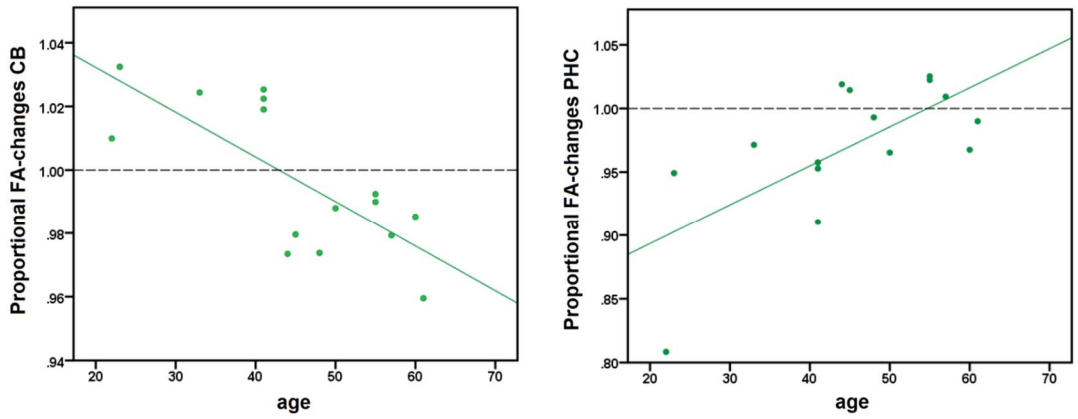

Figure 3.3 Age-dependent FA-changes in the right CB and the left PHC

Age-dependent fractional anisotropy (FA) changes during remission in the right CB (left) and the left PHC (right). Points localized above the dotted line indicate increases in FA, points below the dotted line indicate decreases in FA. In the right cingulum bundle, FA increases are seen in younger patients, while decreases are seen in older patients. In the left parahippocampal cingulum, the reverse is true (i.e., FA *decreases* in younger patients, and *increases* in older patients).

Secondary analyses for the left PHC demonstrated that changes in FA were mainly driven by RaD (main effect time: F (1, 13) = 15.067, p = 0.002, time x age interaction: F (1, 13) = 14.148, p = 0.002). There were neither significant main effects of MD and AD for the left PHC, nor significant main effects of RaD, MD and AD for the right CB.

Main effects of time for mean-FA remained significant when excluding the four bipolar patients (right CB: main effect time: F (1, 9) = 9.106, p =0.015, left PHC:

main effect time: F (1, 9) = 10.448, p =0.01). Further, results remained significant when (in addition to age) we controlled for HAMD-scores at baseline (right CB: F (1, 12) = 13.645, p = 0.003 ; left PHC: F (1, 12) = 7.944, p = 0.016), number of episodes (right CB: F (1, 12) = 11.373, p = 0.006; left PHC: F (1, 12) = 12.73, p = 0.004), duration of illness (right CB: F (1, 12) = 7.282 , p = 0.019; left PHC: F (1, 12) = 10.135, p = 0.008) duration of current episode (right CB: F (1, 12) = 9.765, p = 0.009; left PHC: F (1, 12) = 16.986, p = 0.001) and number of days between the scans (right CB: F (1, 12) = 6.410 , p = 0.026 ; left PHC: F (1, 12) = 19.379, p = 0.001).

There was a positive correlation between percentage of absolute FA-changes and reductions in HAMD scores for the right CB (r = 0.532, p = 0.041, see figure 3.4), but not for the left PHC (r = -0.169, p = 0.548).

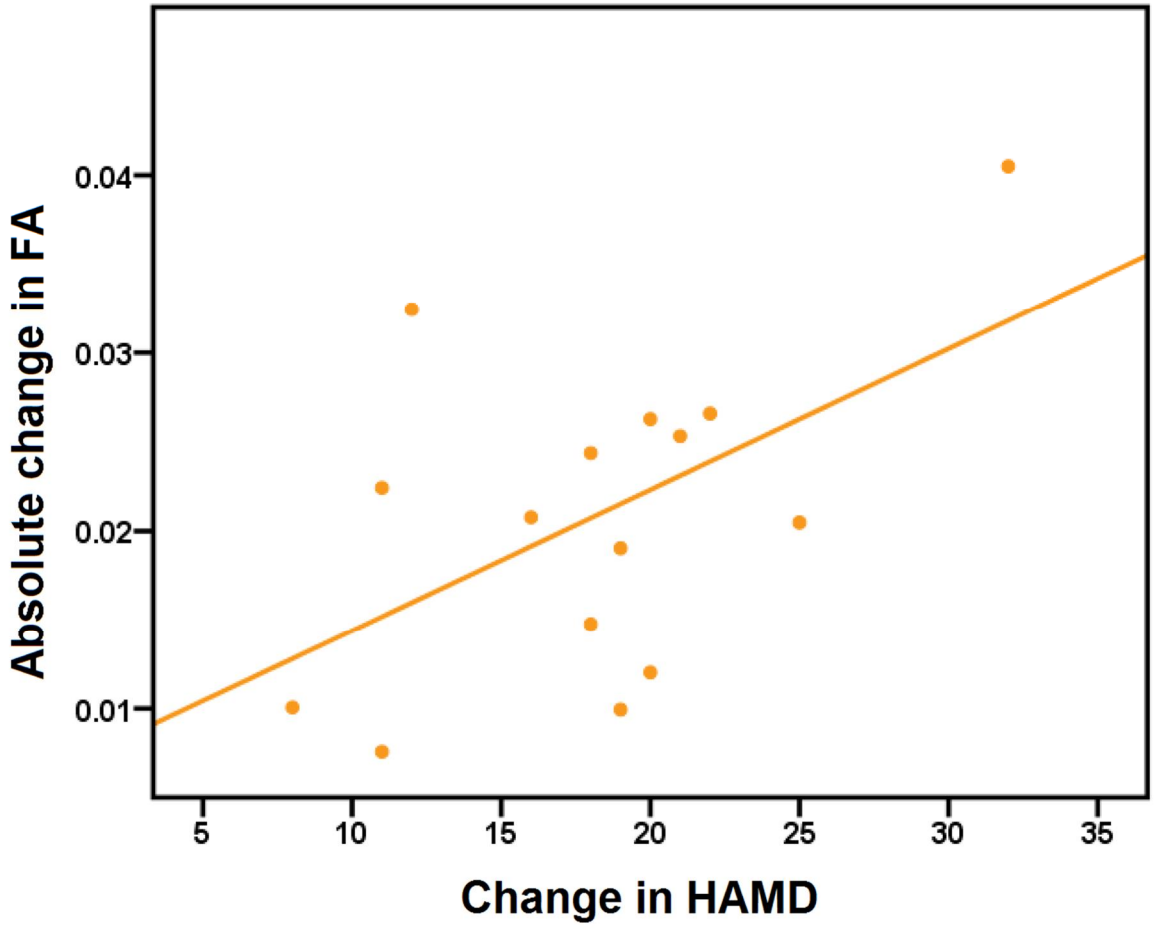

Figure 3.4 Correlation between FA changes and clinical improvement

Positive correlation between absolute fractional anisotropy (FA)-changes (%) and reductions in HAMD-scores for the right CB.

3.5 Discussion

This is the first tract specific longitudinal assessment comparing white matter microstructure between depression and remission. We found a differential age-dependent pattern of mean-FA changes occurring during remission for the right CB and the left PHC. In the right CB, FA increases are seen in younger patients, while decreases are seen in older patients. In the left PHC, the reverse is true. More marked FA-changes in the right CB were associated with more pronounced reductions in HAMD-scores. No FA-changes were found in bilateral UF, slMFB and the fornix, suggesting that these pathways might not undergo remodeling during remission.

We found increases and decreases of FA that depended on age and also on the tract (see pattern of green circles below and above the dotted line for the left PHC and the right CB, figure 3.3). There is accumulating evidence that white matter plasticity extends into old age (Engvig et al., 2012; Lovden et al., 2010). However, at the same time, animal literature suggests that neuroplasticity decreases with age (Blumenfeld-Katzir et al., 2011). Therefore, if some neuroplastic processes decrease, whilst others persist, age-dependent differences of simultaneously occurring neuroplastic processes (e.g. changes in axonal diameter, myelination, and proliferation of glia cells) may in aggregate have had an opposing effect on FA in younger and in older depressed patients of our sample.

During the time interval from depression to clinical remission, we observed decreases of FA in the left PHC in younger patients, but only in a proportion of older patients. One possible explanation is that decreases of mean-FA for the left PHC during remission stem from a more complex fibre orientation due to new sprouting of hippocampal axons. This is indirectly supported by animal literature demonstrating increases of sprouting of hippocampal axons following the administration of electroconvulsive shocks, which are used for electroconvulsive therapy (ECT) (Madhav et al., 2000). ECT is amongst the most effective treatments for severely depressed patients and may lead to remission when other approaches fail (Fink and Taylor, 2007). Therefore, if ECT induces hippocampal sprouting, this neuroplastic process may indeed be associated with or even be directly relevant to the recovery from depression (Madhav et al., 2000). However, hippocampal sprouting of axons decreases with age (Kuhn et al., 1996; Leuner et al., 2007). This may explain why decreases of FA were only consistently observed in the younger patients, while in

older patients FA changes may have been driven by other neuroplastic processes as well.

In the right CB there was a distinctive pattern of FA increases in younger, and FA decreases in older patients, which again may stem from differences in neuroplasticity depending on age (Blumenfeld-Katzir et al., 2011). The percentage of absolute FA-changes in the right CB was positively related to reductions in overall HAMD-scores. This suggests that successful anti-depressive treatment is associated with white matter remodeling of the right CB. Our finding in the CB is also supported by a one-year follow up longitudinal DTI-study that reported FA changes in the ACC in remitters but not in non-remitters (Taylor et al., 2011).

The physiological state between depression and remission differs substantially. Amongst other, lower serum levels of BDNF have been reported consistently during depressive episodes (Karege et al., 2005). This may be associated with impaired neuroplasticity (Duman and Monteggia, 2006). Interestingly, those patients with higher baseline levels of BDNF during depression show a better treatment response (Mikoteit et al., 2014). Therefore, one may speculate whether BDNF may play a role to facilitate white matter remodeling as suggested by our findings of FA changes in the right CB and the left PHC. This assumption is also indirectly supported by findings that BDNF-recpetor polymorphisms increase the risk of white matter microstructure alterations in MDD (Murphy et al., 2012).

A series of imaging studies investigated brain states that distinguish responders from non-responders. In particular the structure and function of the ACC may be predictive of symptomatic improvement during antidepressive therapy (Fu et al., 2004; Keedwell et al., 2009; Mayberg et al., 2000; McGrath et al., 2013; Taylor et al., 2008). Further, one DTI-study found reduced FA in the hippocampus comparing non-responders with responders (Zhou et al., 2011), while others found reduced FA in the cingulum bundle comparing non-remitters with remitters (Korgaonkar et al., 2014). While it is possible that the brain of non-responders differs from the brain of responders, an alternative explanation is that remission is accompanied by neuroplasticity as suggested by our data.

Reduced FA in the slMFB has been reported in melancholic (Bracht et al., 2014) but not in non-melancholic (Bracht et al., 2014) and in remitted MDD patients (Bracht et al., 2015a) (Chapter 2). In our study we did not identify any changes of FA occurring from during the time-span of remitting in the slMFB. This may be due to the fact that most of our MDD-patients did not meet criteria for melancholic depression and

therefore there may not have been any structural changes at baseline. Furthermore, the sample size has been small and there was substantial clinical heterogeneity. Future studies may address this question by selectively investigating a more homogeneous subgroup (e.g. melancholic MDD-patients).

Our data provide further support for the hypothesis that experience and white matter microstructure mutually influence each other (Sagi et al., 2012; Scholz et al., 2009; Zatorre et al., 2012). Accordingly, white matter microstructure may serve as a state marker reflecting the current state of clinical improvement. However, DTI is unspecific for alterations of different sub-compartments of white matter and therefore also lacks sensitivity (Jones et al., 2013b). Therefore, we cannot provide ultimate and entirely conclusive answers regarding the underlying neurobiology of neuroplastic processes. Advanced white matter mapping techniques provide information on some of these measures and therefore offer promise in elucidating the neurobiological underpinnings of our findings (De Santis et al., 2013; Deoni et al., 2008a).

This study is limited by sample size, and a heterogeneous pattern of age and clinical presentations. Therefore, all analyses were controlled for age. Including number of episodes, duration of the disease, depression severity at baseline and number of days between the two scans as additional covariate as well as excluding the four BD patients from the analyses did not alter the results. Further, all patients were on medication. We cannot rule out that medication caused the observed changes in mean-FA. However, the severity of depression symptomatology of our sample necessitated a treatment with medication. Also, the specificity of our finding for the left PHC and the right CB in the absence of any changes for the UF, the slMFB and the fornix contradicts the assumption of global white matter changes being caused by medication as shown in previous studies (Benedetti et al., 2011; de Diego-Adelino et al., 2013). A further tract of interest to look at in future studies is the infero-medial MFB (imMFB). However, the quality of the data was not sufficient to apply the damped Richardson-Lucy algorithm (Dell'acqua et al., 2010) for tractography (see Chapter 2). Thus, we used DTI-based tractography. This did not enable us to reliably reconstruct the imMFB.

In summary our results suggest that during recovery from depression white matter microstructure alterations occurred in two tracts previously associated with the pathobiology of depression. We detected a differential age-dependent pattern of

white matter plasticity in the left PHC and the right CB during the time course of remission. These findings provide initial evidence for the potential of white matter microstructure as a state marker in depression. Future studies should attempt to replicate and extend our findings by investigating more homogeneous clinical and age matched subgroups. Novel white matter mapping techniques may contribute to the identification of specific white matter microstructural sub-compartment changes (De Santis et al., 2013; Deoni et al., 2008a).

4 Myelination of the right parahippocampal cingulum is associated with physical activity in young healthy adults

The work presented in this chapter has been published:

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4.1 Summary

Physical activity (PA) is reduced in depression. Recent evidence suggests that individual differences in physical activity may be associated with individual differences in white matter microstructure and with grey matter volume of the hippocampus. However, little is known about the relationship between physical activity and white matter microstructure of pathways connecting to the hippocampus. This study investigated the association between physical activity and white matter microstructure of the fornix and bilateral parahippocampal cingula (PHC). A total of 33 young, healthy adults underwent magnetic resonance imaging (MRI). High angular resolution diffusion-weighted imaging (HARDI) and multi-component relaxometry MRI-scans (multi-component driven equilibrium pulse observation of T1 and T2 (McDESPOT)) were acquired for each participant. Activity levels (AL) of participants were calculated from 72-hour actigraphy recordings. Tractography using the damped Richardson Lucy (dRL) algorithm was used to reconstruct the fornix and bilateral PHC. The mean fractional anisotropy (FA) and the myelin water fraction (MWF), a putative marker of myelination were determined for each pathway. A positive correlation between both AL and FA and between AL and MWF were hypothesized. MWF in the right PHC was significantly correlated with AL ($r = 0.482$, $p = 0.007$), while there were no significant correlations between FA and AL for any of the three tracts. Thus, our results provide initial *in vivo* evidence for an association between myelination of the right PHC and physical activity in young healthy adults. Our results suggest that MWF may not only be more specific but also more sensitive than FA to detect white matter microstructural alterations.

4.2 Introduction

4.2.1 Physical activity, white matter microstructure and depression

Psychomotor retardation is a key feature of major depressive disorder (Schrijvers et al., 2008). It may distinguish clinical subtypes and it may be associated with response to some antidepressants (Calugi et al., 2011; Schrijvers et al., 2008). PA is known to be reduced during depressive episodes (Razavi et al., 2011). By means of reduced interest in daily activities it forms a diagnostic criterion of depression according to the diagnostic and statistical manual of mental disorders (DSM-IV). In addition slowing of movements is one of the diagnostic criteria according to the international classification of diseases (ICD-10). In many cases physical activity increases during the time-span from depression to remission, as shown in participants being investigated in this thesis (see the significant increase of activity levels comparing MDD-patients during depression and following remission, table 3.1, Chapter 3).

In healthy participants PA has been shown to be associated with improved cognitive performance (Sibley and Etnier, 2003), executive functioning (van der Niet et al., 2014) and pleasurable affective responses (Bartlett et al., 2011; Ekkekakis et al., 2005), all functions being impaired during depressive episodes. Thus, PA contributes to clinical recovery from depression and exercise programs form an integral part of antidepressive treatment (Cooney et al., 2014; Mead et al., 2009).

So far, the focus of this thesis has been on the neurobiology of the reward system in depression. The reward system may be directly linked to motor behaviour given that much of our goal-directed actions are motivated by incentives, which are evaluated within the reward system (Chapter 1, (Der-Avakian and Markou, 2012). Neuroimaging studies have shown that there are not only structural and functional changes of the reward circuit in depression (Chapter 1), but also changes that are directly linked to psychomotor retardation in depression (Bracht et al., 2012a; Walther et al., 2012a; Walther et al., 2012b). Nevertheless to date ï even in healthy subjects- very little is known on the effect of PA on the structure of the brain. Consequently, there has been an increasing interest in this topic.

Diffusion Tensor Magnetic Resonance Imaging (DTI) enables a non-invasive *in vivo* assessment of brain white matter microstructure (Basser et al., 1994). Diffusion

properties such as FA indirectly reflect the extent to which the diffusion of water molecules in the brain tissue is preferentially hindered along one direction compared to others, which in turn provides information on the underlying white matter microstructure (Basser and Pierpaoli, 1996). A previous DTI study found a positive correlation between aerobic fitness and FA in the uncinate fasciculus and cingulum bundle (Marks et al., 2007). Findings in segments of the middle cingulum were replicated by the same group using objective markers of aerobic fitness (Marks et al., 2011). Walther et al. (2010), using 24 hour recordings of actigraphy as an objective measure of motor activity to assess PA, found a positive association between AL and FA in the right superior longitudinal fasciculus (SLF) and cingulum bundle, and a negative correlation between AL and FA in the left corticobulbar tract, right posterior corpus callosum and left SLF (Walther et al., 2010). Further, associations between PA and white matter microstructure were identified in the corticospinal tract (Herting et al., 2014), the corpus callosum (Johnson et al., 2012) and in prefrontal, parietal and temporal brain regions (Voss et al., 2013). Thus, there is converging evidence that differences in PA are associated with differences in white matter microstructure in multiple brain regions.

4.2.2 Hippocampal pathways and physical activity

The hippocampus is a further region of particular interest regarding the structural correlates of PA. Animal research suggests strongly that PA induces neuroplastic processes in the hippocampus. For example, it has been shown that wheel-running in mice increases cell proliferation in the dentate gyrus (van Praag et al., 1999a; van Praag et al., 1999b; van Praag et al., 2005), and induces increases in BDNF, which supports survival of neurons, localized in hippocampal areas (Berchtold et al., 2005; Neeper et al., 1995). BDNF has been also shown to induce myelination in white matter pathways in both animal and in *in vitro* studies (Wong et al., 2014; Xiao et al., 2010). In elderly humans, PA was associated with increased volumes in bilateral hippocampi (Erickson et al., 2009). This finding was corroborated by findings that a PA exercise program (in contrast to a stretching program) led to increases in volume in the hippocampus (Erickson et al., 2011). Moreover, MD has been shown to be reduced in elderly master athletes in a region incorporated in the parahippocampal cingulum in comparison with a less fit age-matched control group (Tseng et al., 2013), while a reduction in FA was reported in sedentary older adults in a recent DTI study (Burzynska et al., 2014). In contrast, decreases of FA were associated with

increased PA in major depressive disorder while no association was found in healthy controls (Walther et al., 2012b).

4.2.3 Diffusion properties and myelin water fraction

Most previous studies using DTI-based diffusion properties such as FA for the assessment of white matter microstructure are limited by the lack of specificity for white matter sub-compartments. For instance, increases in FA may stem from reductions in axonal diameter, higher axonal density, higher myelination, and/or lower intra-voxel orientational dispersion (Beaulieu, 2002; Jones et al., 2013b). Thus, DTI-based measures on their own do not allow for a sub-compartment specific, and therefore neurobiologically meaningful, interpretation of the data. Moreover, the lack of specificity may lead to conflicting results across studies. For instance, while greater myelination and larger axonal diameter both increase conduction velocity, they have opposite effects on FA. The development of multicomponent driven equilibrium single pulse observation of T1 and T2 (McDESPOT) allows for rapid acquisition of data to produce whole brain myelin water fraction (MWF) maps which have been shown to correlate with myelination (Deoni et al., 2008a; Hurley et al., 2010; Laule et al., 2006; MacKay et al., 1994; Moore et al., 2000). Thus, the measure of MWF represents a significant step forward for the interpretability of previously reported changes in white matter, compared to reliance on DTI alone. Furthermore, while DTI metrics can be sensitive to differences in myelin (Song et al., 2002) it is worth noting that in genetically modified mice in which myelin has very little presence (e.g. the Shiverer mouse), the fractional anisotropy is only around 15% lower than in a wild type mouse (Song et al., 2002). Consequently, changes in myelin of a few percent would have a very small impact on FA. Conversely, as measures such as MWF are thought to be more directly associated with myelin, their sensitivity to myelin changes should be more marked.

4.2.4 Aims of the study and hypothesis

The present study explored the association between PA and white matter microstructure of the two main hippocampal pathways: the fornix and the PHC. The fornix is the main efferent pathway of the hippocampus projecting to the mammillary bodies (Nieuwenhuys et al., 2007). The PHC forms part of the cingulum bundle and

contains predominantly afferent projections from the posterior parietal cortex (Goldman-Rakic et al., 1984; Jones et al., 2013a; Mufson and Pandya, 1984). In the present study we use FA as a well-established (though unspecific) marker of white matter microstructure. Further, we use MWF as a potentially more specific measure of myelination.

We hypothesize a positive correlation between FA and AL, and a positive correlation between MWF and AL, in the fornix and in bilateral PHC. We assume that due to the specificity for myelination, i.e., being less susceptible to confounding microstructural differences such as axonal diameter, density and axonal orientational dispersion than DTI metrics, (De Santis et al., 2014) MWF will be a more sensitive marker than FA to detect associations between individual differences between PA and white matter microstructure.

4.3 Methods

4.3.1 Participants

All participants were recruited through the School of Psychology, Cardiff, Wales, United Kingdom. All participants were undergoing or had previously completed a university degree course, were right handed as assessed with the Edinburgh Handedness Inventory (Oldfield, 1971) and of Caucasian origin. Exclusion criteria were a current episode or a history of neurological and psychiatric disorders, drug or alcohol abuse and medication that may have an impact on the structure of the brain. For assessment, the general health questionnaire was used (Goldberg and Huxley, 1980). Since training may impact the structure of the brain we also excluded professional athletes, musicians and those at competitive amateur sport levels (Bengtsson et al., 2005; Hanggi et al., 2010; Scholz et al., 2009). A total of thirty-three participants was recruited (19 female, 14 male). Participants had a mean-age of 25.5 ± 4.2 years. All participants provided written informed consent in order to take part in the study and received monetary compensation. The study had been approved by the local ethics committee of the School of Psychology, Cardiff (EC.13.07.02.3491RA).

4.3.2 Actigraphy

Participants wore an Actiwatch (Cambridge Neurotechnology, Inc., Cambridge, UK) on the left wrist for 72 consecutive hours. Activity counts were stored in 5 second intervals. Participants provided an activity protocol stating the kind of daily activities and wake time. AL) (the cumulated activity counts during wake time divided by the net recording time in hours) were calculated separately for each day. Activity analyses were restricted to wake time. Mean-AL was calculated by averaging AL over the three consecutive days. The left wrist was chosen because AL of the non-dominant arm reflects whole body movements without impact of manual fine motor activities (Middelkoop et al., 1997). Protocols were checked for consistency between reported activities and AL measures. Almost identical approaches have been repeatedly used in previous studies e.g. (Bracht et al., 2012b; Razavi et al., 2011; Walther et al., 2009).

4.3.3 Structural MRI scanning

T1-weighted structural scans were acquired using an oblique axial, 3D fast-spoiled gradient recalled sequence (FSPGR) with the following parameters: TR=7.9ms, TE=3.0ms, inversion time=450ms, flip angle=20°, 1 mm isotropic resolution, with a total acquisition time of approximately 7 minutes.

4.3.4 Diffusion MRI scanning

High angular resolution diffusion-weighted imaging (HARDI) data were acquired in the Cardiff University Brain Research Imaging Centre (CUBRIC) on a 3 T GE Signa HDx system (General Electric, Milwaukee, USA) using a cardiac-gated peripherally gated twice-refocused spin-echo Echo Planar Imaging (EPI) sequence, with effective TR/TE of 15R-R intervals / 87 ms. Sets of 60 contiguous 2.4 mm thick axial slices were obtained, with diffusion-sensitizing gradients applied along 30 isotropically distributed (Jones et al., 1999) gradient directions (b-value = 1200 s/mm^2). The field of view was 23 × 23 cm; and the acquisition matrix was 96 × 96, resulting in data acquired with a 2.4 × 2.4 × 2.4 mm isotropic resolution. Following zero-filling to a 128×128 in-plane matrix for the fast Fourier transform, the final image resolution was 1.8 × 1.8 × 2.4 mm. A parallel acceleration (ASSET) factor of 2 was used. Acquisition time was approximately 12 minutes.

4.3.5 McDESPOT scanning

The McDESPOT protocol consists of a combination of sagittally oriented SPGR, balanced steady-state free procession (bSSFP) and inversion-recovery prepared SPGR (IR-SPGR) sequences (Deoni et al., 2008c; Deoni et al., 2008d). All three sequences were acquired with a FOV of 220 mm; 1.7 mm × 1.7 mm × 1.7 mm voxels, with frequency encoding in the superior-inferior direction for a total scan time of approximately 8 minutes. mcDESPOT protocol (spoiled gradient recalled, or SPGR, acquisitions: TE = 2.1 ms, TR = 4.7 ms, flip angles = [3°, 4°, 5°, 6°, 7°, 9°, 13°, 18°]; balanced Steady-State Free Precession, or bSSFP, acquisitions: TE = 1.6 ms, TR = 3.2 ms, flip angles = [10.6°, 14.1°, 18.5°, 23.8°, 29.1°, 35.3°, 45°, 60°], spatial resolution 1.7 mm isotropic, acquisition time 12 min). bSSFP acquisitions were repeated with and without 180° RF phase alteration to remove SSFP banding artefacts and SPGR and IR-SPGR acquisitions were used to correct B_0 and B_1-induced errors in the derived MWF estimates.

4.3.6 McDESPOT Data Pre-Processing

SPGR and bSSFP images for each participant were linearly coregistered using an affine (12 degrees of freedom) technique based on mutual information to the first image in the sequence to correct for interscan and intrascan motion (Jenkinson and Smith, 2001). SPGR and IR-SPGR images were used for DESPOT1 with High-speed Incorporation (DESPOT1-HIFI) of RF Field Inhomogeneities processing as described in (Deoni, 2007; Deoni et al., 2006b), resulting in B1 field and quantitative T1 maps. These B_1 field and T1 maps were used in the subsequent calculation of B_0 field and T2 maps using two phase-cycled bSSFP data using the DESPOT2 with full modeling (DESPOT2-FM) algorithm (Deoni et al., 2004). Combining SPGR, IR-SPGR and SSFP sequences allowed for the estimation of the multi-component three pool DESPOT model (Deoni et al., 2013; Deoni et al., 2008b; Deoni et al., 2008c). Alongside other metrics not studied here (myelin water residence time and intra- and extra-cellular (IE) water and myelin water T1 and T2), this model provides whole brain estimates of the myelin water fraction (MWF).

4.3.7 Post-processing of McDESPOT data

A synthetic-T1 image was computed from the quantitative T1 map (arising from the DESPOT1 data) for each subject assuming the same imaging parameters used to generate the FSPGR T1-weighted image (Deoni et al., 2006a). This effectively creates a template in MWF space with the same contrast as the target T1-weighted image. The synthetic T1-weighted image of each participant was then warped to the corresponding T1-weighted structural scan using the FNIRT non-linear registration tool (Jenkinson et al., 2002). The computed warps were then applied to the MWF map to transform it into the same space as the structural T1-weighted image.

4.3.8 Diffusion MRI data pre-processing

Data were analysed using *ExploreDTI* 4.8.3 (Leemans et al., 2009a). Eddy-current induced distortion and motion correction was performed using an affine registration to the non-diffusion-weighted B0-images, with appropriate re-orienting of the encoding vectors (Leemans and Jones, 2009). Field inhomogeneities were corrected for using the approach of (Wu et al., 2008). The diffusion weighted images (DWIs) were non-linearly warped to the T1-weighted image using the fractional anisotropy map, calculated from the DWIs, as a reference. Warps were computed using Elastix (Klein et al., 2010) using normalized mutual information as the cost function and constraining deformations to the phase-encoding direction. The corrected DWIs were therefore transformed to the same (undistorted) space as the T1-weighted structural images. A single diffusion tensor model was fitted to the diffusion data in order to compute quantitative parameters such as FA (Basser et al., 1994). Following the method of Pasternak et al. (Pasternak *et al.*, 2009; Metzler-Baddeley *et al.*, 2012), a correction for free water contamination of the diffusion tensor based estimates was applied.

4.3.9 Tractography

Tractography was performed using *ExploreDTI* (Leemans et al., 2009a). Whole brain deterministic tractography was performed following peaks in the fibre orientation density function (fODF) reconstructed from the damped Richardson Lucy algorithm (dRL) (Dell'acqua et al., 2010; Jeurissen et al., 2013). The dRL algorithm estimates multiple fibre orientations in a single voxel and therefore provides a more accurate diffusion profile than it is the case for DTI-based methods estimating only one fibre orientation per voxel. For each voxel in the dataset, streamlines were initiated along any peak in the fibre orientation density function (fODF) that

exceeded an amplitude of 0.05. A streamline, uniform step-size, algorithm based on that of (Basser et al., 2000), but extended to multiple fibre orientations within each voxel (Jeurissen et al., 2011) was used for tractography. Each streamline continued in 0.5mm steps following the peak in the fODF that subtended the smallest angle to the incoming trajectory. Termination criteria were an angle threshold > 45° and fODF amplitude < 0.05.

4.3.10 Tract reconstruction

Tract ówaypointôregions were drawn manually by one experimenter (T.B.) based on anatomical landmarks. The fornix and bilateral PHC (see figure 1) were reconstructed as described in Chapter 3. For reconstruction of the fornix, a coronal region of interest (ROI) was placed around the columns of the fornix four slices posterior to the anterior commissure (Bracht et al., 2015b). For reconstruction of bilateral PHC one horizontal ROI was placed at the height of the most ventral point of the splenium, and a second ROI was placed four slices above (Jones et al., 2013a; Metzler-Baddeley et al., 2013). For each subject, the anatomical course of each tract was checked carefully. Mean-FA was derived for each reconstructed tract. In addition, the average MD, AD and RaD were computed for each tract in order to follow up any group differences seen in FA, our primary outcome measure. Further, mean-MWF was sampled along the tracts. The latter was derived from the MWF-images that had been warped to the T1ï weighted structural image.

4.3.11 Statistical analyses

Statistical analyses were performed using SPSS22 (SPSS, Inc., Chicago, Illinois). First, normal distribution of mean-AL, FA and MWF-values was confirmed using Shapiro-Wilk-Tests. Second, Pearson correlations between the mean-AL and FA of bilateral PHC and the fornix were calculated. Third, correlations between mean-AL and MWF, our measure for myelination, were calculated for each of the three hippocampal pathways. We applied a strict Bonferroni correction for multiple comparisons. Thus the level of significance was set at $p < 0.0083$ (0.05 divided by the number of tests, $n = 6$). In pathways where significant correlations were detected we additionally controlled for age and gender calculating separate partial correlation with age and gender as covariates.

4.4 Results

4.4.1 Activity levels

One participant had to be excluded from the analyses because their actigraphy recording was incomplete and there had been inconsistencies between reported activities and recorded AL. Thus a total of 32 participants with AL-recordings remained. AL was normally distributed for each of the three single days and for mean-AL (averaged over the three days). Repeated measure analyses revealed no significant differences of AL for the three consecutive days ($F(2, 30) = 0.37$, $p = 0.70$). AL-values were as follows: AL day 1 = 20513 ± 6081, AL day 2 = 21496 ± 8000, AL day 3 = 21516 ± 6174, and mean-AL = 21174 ± 5345. Men and women did not differ regarding AL for any of the days or regarding mean-AL.

4.4.2 Correlations between activity levels and white matter microstructure

For each of the tracts, FA and MWF values were normally distributed. Across the 32 participants there were no significant correlations between mean-AL and FA for the fornix ($r = 0.232$, $p = 0.201$), left ($r = -0.123$, $p = 0.503$) or right ($r = 0.047$, $p = 0.800$) PHC.

Two participants had to be excluded from the McDESPOT analyses because of incomplete data acquisition, and thus 30 scans remained. There was a positive correlation between mean-AL and MWF for the right ($r = 0.482$, $p = 0.007$) but not for the left ($r = 0.069$, $p = 0.718$) PHC (see figure 2). Further, there was a non-significant trend for a positive correlation between MWF of the fornix and mean-AL ($r = 0.325$, $p = 0.079$). The correlation between the right PHC and mean-AL remained significant after controlling for age ($r = 0.531$, $p = 0.003$) and for gender ($r = 0.483$, $p = 0.008$). In order to statistically demonstrate the larger magnitude of the correlation between AL and MWF of the right PHC in comparison to the correlation between AL and FA of the right PHC Fisherôs r-to-z transformation was used ($z = 3,6$, $p = 0.0003$) (Steiger, 1980) (http://quantpsy.org/corrtest/corrtest2.htm).

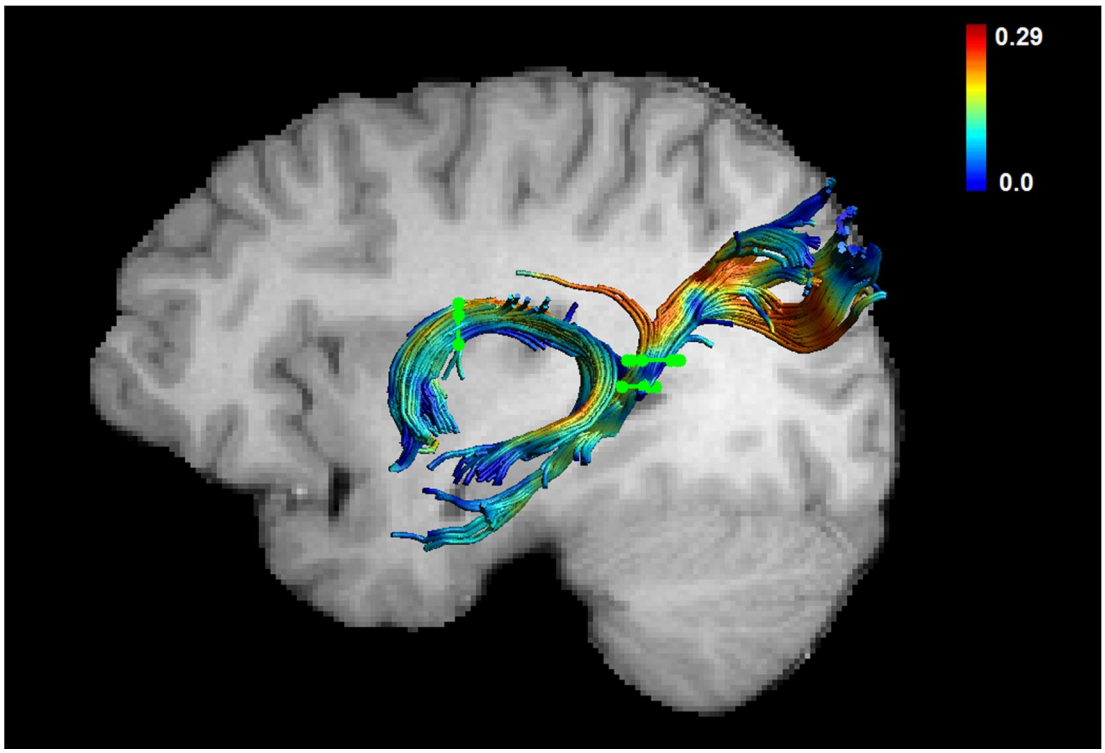

Figure 4.1 Myelin water fraction sampled across the fornix and the PHC

Myelin water fraction sampled across the fornix and the PHC. Tract ñwaypointò regions are visualized in green.

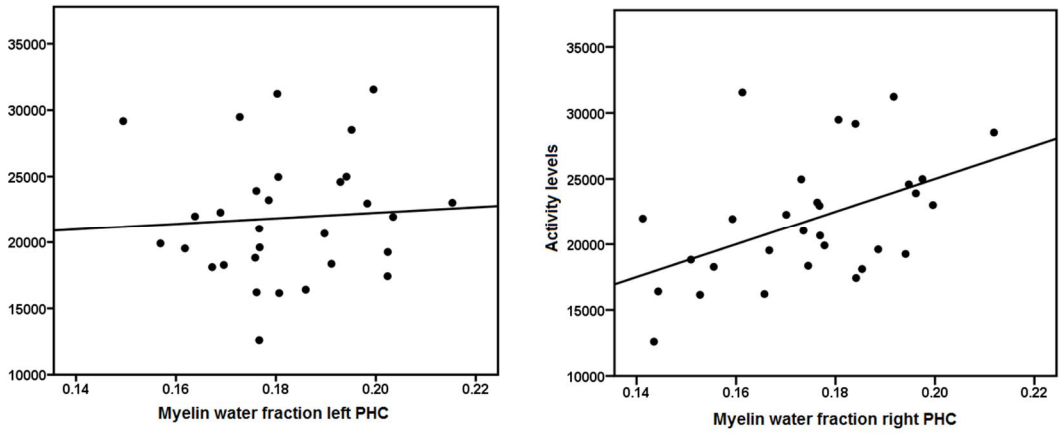

Figure 4.2 Correlation between AL and MWF for left and right PHC

Correlation between activity level (AL) and the myelin water fraction (MWF) for the left (r = 0.069, p = 0.718, left side) and the right (r = 0.482, p = 0.007, right side) parahippocampal cingulum (PHC).

4.5 Discussion

This is the first tract-specific study linking white matter microstructure of hippocampal pathways to PA activity. This is also the first study investigating the association between PA and MWF, a more specific measure of myelination than FA. While correlations between FA and AL did not yield significant results for any of the tracts, there was a significant correlation between AL and MWF for the right PHC. Thus, our results suggest that higher PA is associated with higher myelination in the right PHC. We infer, therefore, that MWF not only represents a more specific marker for myelination but is also a more sensitive marker than FA for detecting associations between white matter microstructure and PA. Our results contribute to the understanding of brain-behaviour associations and inter-individual variance even in a highly homogeneous group of young adults.

4.5.1 The role of myelin

Our findings suggest that higher physical activity is associated with increased myelination of the right PHC. Myelination is mediated by oligodendrocytes, glia cells that encapsulate axons and facilitate fast and saltatory conduction of electrical impulses. Myelin increases conduction velocity which in turn may facilitate more efficient information processing (Fields, 2008). Animal studies clearly suggest that experience influences the degree of myelination. For instance, stress during pregnancy in rodents increases myelination in the offspring (Wiggins and Gottesfeld, 1986). Moreover, the degree of social interactions and the number of play objects leads to increases in myelination (Bennett et al., 1964; Markham and Greenough, 2004; Szeligo and Leblond, 1977). *In vitro* studies also suggest that neuronal activity by means of neurotransmitter release promotes myelin induction (Demerens et al., 1996; Wake et al., 2011). Moreover, electrical stimulation of the premotor cortex in mice has also been shown to cause increases in myelination which were associated with improved motor function of the corresponding limb (Gibson et al., 2014). Thus, while our study design does not allow for statements regarding causalities of the observed association between MWF and AL, multiple lines of evidence suggest that experience and behaviour indeed induce remodelling of myelination of the brain (Fields, 2008).

4.5.2 Myelin and myelin water fraction

In humans, the MWF can be used for an *in vivo* assessment of myelination. One previous study used MWF as a marker of myelination and found a pattern of myelination in infants that showed striking similarities with what is known from post-mortem studies (Deoni et al., 2011). In addition, studies in demyelinating neurological disorders such as multiple sclerosis strongly suggest the validity of MWF as a measure for myelination (Kitzler et al., 2012; Kolind et al., 2012). In one longitudinal study during early childhood changes of MWF correlated positively with performance measures such as gross motor behaviour, visual reception and receptive language (Dean et al., 2014). MWF has also been shown to be associated with disease severity in multiple sclerosis (Kolind et al., 2012). Finally, the most compelling evidence for the assumption that MWF indeed measures myelin stems from comparisons between MWF maps derived from a shaking pup myelin mutant and control animals (Hurley et al., 2010) and imaging studies demonstrating correlations between MWF and histopathology in multiple sclerosis (Laule et al., 2006; Moore et al., 2000). Thus, there is ample evidence that MWF does truly correlate with myelination and that this measure may represent a clinical and functional useful marker to detect associations of brain structure and function.

4.5.3 Associations between physical activity and hippocampal anatomy

In light of previous studies investigating the role of the hippocampus for aerobic exercise our finding in the PHC is highly plausible. In mice, wheel running has been shown to induce an increase of the number of axons (Pereira et al., 2007; van Praag et al., 1999a; van Praag et al., 1999b). Further, in both mice and in humans physical activity led to increases of the cerebral blood flow (CBF) (Pereira et al., 2007) which has been shown to induce neurogenesis in the dentate gyrus of these animals (Pereira et al., 2007). Wheel running in mice also induces increases in brain-derived neurotrophic factor (BDNF), a growth factor that supports survival of neurons and induces myelination (Berchtold et al., 2005; Neeper et al., 1995; Wong et al., 2014; Xiao et al., 2010). Further, there is converging evidence from neuroimaging studies that physical activity increases grey matter volume of the hippocampus (Chaddock et al., 2010; Erickson et al., 2012; Erickson et al., 2009; Pajonk et al., 2010) which may impact plasticity of white matter microstructure as well. Thus, studies in animals and volumetric neuroimaging studies in humans strongly support our finding that

physical activity is associated with higher myelination in the PHC, the main afferent pathway of the hippocampus.

4.5.4 Comparison with previous DTI studies and lateralization

In our study we found a selective positive correlation between PA and MWF in the right PHC. We did not find any associations between physical activity and diffusion properties in our young and healthy sample. The absence of a correlation between FA und PA is in line with a voxel-based DTI study of (Walther et al., 2012b) who found no association between AL and FA in healthy controls in the PHC. However, there was a negative association of FA and AL in major depressive disorder in the left PHC (Walther et al., 2012b). A whole brain tract-based spatial statistics (TBSS) (Smith et al., 2006) study found reduced MD in physically fit older adults compared to a less fit control group in a region incorporating the PHC localized in the left hemisphere as well (Tseng et al., 2013). However, PA was not associated with FA. On the other hand (Burzynska et al., 2014) reported a decrease of FA in sedentary old adults averaged across bilateral PHC using TBSS. Since DTI-based diffusion properties are not specific for myelin and completely different populations have been investigated in previous studies (Burzynska et al., 2014; Tseng et al., 2013; Walther et al., 2012b) comparability of the latter findings with our study in young and healthy participants is aggravated. Nevertheless, in light of previous results in the left hemisphere (Tseng et al., 2013; Walther et al., 2012b) our specific finding for the right hemisphere is surprising. One possible explanation is that in elderly populations and in depression brain-structure behaviour associations of the right hemisphere that can be seen in our young and healthy sample are impaired and compensated for by the left hemisphere that is not involved in young and healthy participants.

4.5.5 Translational aspects for the neurobiology of depression

In Chapter 3 we found age-dependent FA changes to occur in the left PHC during the time-span from depression to remission. Participants of this study (Chapter 3) did not only recover from depression, they also significantly increased their activity levels (Chapter 3, Table 3.1). Thus, there may be associations between increases in PA, clinical recovery from depression and structural remodelling of the PHC. Reduced FA of the right PHC has also been described during depressive episodes (e.g. (Zhu et al., 2011). One possible explanation is that those FA reductions are

caused by reductions in myelin. When remitting this reduction in FA may be reversed as a consequence of physical activity increasing myelination. It would be of great interest to address this question with help of MWF maps and to investigate if putative reductions of MWF during depressive episodes may be reversed from depression to remission. A further key question is to investigate if these putative changes may be reversed with help of exercise interventions.

4.5.6 Inconsistencies in the literature

Previous studies indicate associations between PA and white matter microstructure of hippocampal pathways (Burzynska et al., 2014; Tseng et al., 2013; Walther et al., 2012b). However, there are inconsistencies regarding identified diffusion properties (e.g. FA and MD), lateralization and the directionality of associations between PA and diffusion properties. In part, this may be owed to differences in study populations. It is possible that in different populations associations between brain structure and behaviour are reflected by changes in different sub-compartments of white matter microstructure (e.g. changes in axonal diameter, density or myelination) that may in aggregate have different effects on different DTI-based indices (such as FA and MD). However, due to the lack of specificity of DTI-based metrics for white matter sub-compartments this cannot be disentangled. Therefore, the myelin specific measure of MWF represents a significant step forward for the interpretability of white matter neuroimaging studies. A further explanation for those discrepancies is that age impacts on white matter microstructure (Lebel et al., 2010) and neuroplasticity of the PHC (see Chapter 3, (Bracht et al., 2015b)). Thus, it is possible that in our young sample changes predominantly occur in myelination which only has a subtle effect on FA (Song et al., 2002), while findings in diffusion properties in elderly populations may be the result of different neuroplastic processes (e.g. neuroplasticity of the axons) (Burzynska et al., 2014; Tseng et al., 2013). Moreover, contrasting results between studies may be owed to differences in methodological approaches. For instance, tractography approaches may be more sensitive than voxel-based analyses or regions of interest (ROI)-analyses to detect tract-specific group differences (Bracht et al., 2015a; Bracht et al., 2014; Kanaan et al., 2006; Keedwell et al., 2012).

4.5.7 Summary and conclusions

Our findings suggest that higher PA is associated with higher myelination of the right PHC. We combined an advanced tract-specific approach (dRL) with a myelin specific measure that enables us to draw anatomically meaningful conclusions from our findings (Dell'acqua et al., 2010; Deoni et al., 2008a). A further strength of the study is the homogeneous sample that reduces much of the variance that otherwise is difficult to control for.

Our results substantially extend previous findings on associations between PA and white matter microstructure. Most importantly, we provide a more myelin-specific measure that allows for a more neurobiologically meaningful interpretation of our data. Furthermore, we chose a tractography-based approach that (in contrast to automated voxel-based approaches) takes individual differences of the course of anatomical pathways into account, and combines multiple samples into the estimate, increasing the statistical sensitivity (Bells et al., 2011). Since the applied dRL-tractography algorithm estimates multiple fibre orientations within a single voxel, inaccuracies that lead to spurious reconstructions if applying DTI-based tractography can be diminished (Dell'acqua et al., 2010).

Our study is limited by the cross-sectional study design, which does not allow us to determine whether physical activity influences white matter microstructure or whether white matter microstructure impacts on motor behaviour. Longitudinal studies are required to address this research question (Scholz et al., 2009). Furthermore, advanced white matter mapping techniques with specificity for axonal properties (e.g. density, diameter) may complement our myelin specific findings (Assaf and Basser, 2005).

5 General discussion

5.1 Anatomical, clinical and functional considerations

The first chapter focused on the existing literature of DTI-studies of the reward system. Findings vary across study populations and methods being used. Very few studies looked at healthy participants at familial risk for developing depression. Those studies point to structural alterations of the CB in this subgroup. In the absence of longitudinal data it remains unclear whether such structural alterations indicate vulnerability or resilience for depression. Also, given that only two studies have investigated this question, findings are very preliminary in nature and future replication studies are required for confirmation. During acute depression reduced FA in the UF has been identified quite consistently. Out of the tracts investigated in this thesis (CB, UF and slMFB) the largest number of studies has focused on this tract ï using different methodological approaches. Therefore, conclusions regarding the UF have a greater degree of evidence, than it is the case for CB and slMFB. Given that the UF connects prefrontal brain regions with the amygdala, which form essential relay stations of the reward circuit that have shown altered activity during depression, this finding is also highly plausible from a functional point of view (Epstein et al., 2006; Keedwell et al., 2005; Smoski et al., 2009; Zhang et al., 2013). However, the most novel insights of this thesis concern the slMFB. The slMFB is at the very core of the reward system because (amongst other functions) it mediates dopaminergic projections from the VTA to the NAcc and to the orbitofrontal cortex, which can be regarded as the most specific brain regions contributing to reward processing (Haber and Knutson, 2010). In contrast to the CB and the UF, which were amongst the first pathways being described using tractography the slMFB has only be described for the first time in 2009 by Coenen and colleagues (Coenen et al., 2009). Coenen and colleagues described two different branches (imMFB and slMFB). The imMFB corresponds closely to what is known from animal studies and reflects projections from the VTA to the hypothalamus and NAcc with some fibres proceeding to the basal forebrain. Coenen and colleagues stated that the slMFB includes far reaching projections to prefrontal brain regions (including OFC and dlPFC) that may be specific to the human brain and may be the result of the more complex folding of the forebrain in humans (Coenen et al., 2012). However, although this slMFB has not been described in the animal literature strong direct connection pathways between the VTA and the OFC have been demonstrated in

ample tract tracing studies in animals (Geeraedts et al., 1990a, b; Nieuwenhuys et al., 1982; Veening et al., 1982). Thus, while the nomenclature of the slMFB is novel in my opinion there is little doubt that the connection pathways of the slMFB do indeed exist in animals as well. In particular a study of Coenen and colleagues that linked hypomanic side effects of deep brain stimulation of the subthalamic nucleus (which is located adjacent to the slMFB) in a Parkinson's patient to an accidental stimulation of the slMFB has given rise to research in depression focusing on this specific pathway (Coenen et al., 2009). Chapter 1 makes an essential contribution to the literature because the literature is searched for findings of VBA- and TBSS studies that may actually have identified changes along the course of the slMFB either before its first description using DTI-based tractography or without referring (or being aware) of this fibre bundle. Due to the crossing of different fibre populations in single voxels and due to the proximity of different pathways (e.g. ATR and slMFB) voxel-based approaches (VBA and TBSS) provide less reliable anatomical tract-specific information than tractography studies do. The number of VBA and TBSS studies identifying changes within the ALIC without referring to the slMFB is surprisingly high. Further, it is clearly noteworthy, that changes along the anatomical course have been in particular found in severely depressed patients and in treatment-resistant depression (Bracht et al., 2014; de Diego-Adelino et al., 2014; Guo et al., 2012; Peng et al., 2013). In 2014 tractography was used for the first time to reconstruct specific segments of the MFB in order to compare white matter microstructure between MDD and HC (Bracht et al., 2014). Region-to-region anatomical connection pathways between VTA, NAcc, mOFC, lOFC and dlPFC were reconstructed. Reduced FA was found in (severely) melancholic depressed patients in comparison to a non-melancholic depressed group and a group of healthy controls. Reduced FA was also associated with higher depression rating scale scores and more pronounced anhedonia providing further evidence for a key role of the slMFB in severe depression. The observation of structural differences between different clinical populations illustrates the need to investigate homogeneous and clinical meaningful subgroups. In order to derive tract specific conclusions it is of utmost importance to use tractography approaches. In keeping with this assumption Chapter 2 investigates a highly homogeneous group of young healthy women being matched for age and IQ comparing a subgroup with a history of depressive episode versus those without a history of a depressive episode. While the identified correlation between FA and hedonic tone, the capacity to derive pleasure from rewarding experiences, further supports the central role of the slMFB for reward processing we did not find any group differences between the groups with

and without a history of depressive episodes. This suggests that white matter microstructure alterations may only be present in (severe) depression.

5.2 Reconstruction of the medial forebrain bundle

In Chapter 2 I separately reconstructed the two branches of the MFB (imMFB and slMFB). I applied dRL, an advanced tractography approach estimating multiple diffusion directions within a single voxel providing a greater degree of anatomical validity and sensitivity to pick up pathways than it is the case for DTI-based tractography (Dell'acqua et al., 2010). A robust approach is described how to best delineate the two branches of the medial forebrain bundle (imMFB and slMFB) based on anatomical landmarks that can be clearly identified (Chapter 2). Furthermore, I specifically reconstruct those segments that emanate from the VTA aiming to capture the most relevant fibre pathways for reward processing. While previous studies reconstructed both branches of the MFB in this thesis imMFB and slMFB are separately reconstructed and consequently, its diffusion properties are explored independently.

A series of attempts not described in this thesis for the sake of readability have been made to systematically identify the best way for reconstructing these two branches. Using whole brain DTI-based tractography I failed to reconstruct the imMFB in several subjects. Data quality of data sets using 42 directions was sufficient for DTI-based tractography but not to use the dRL-algorithm. Consequently I struggled to reconstruct the imMFB in these data sets. From my experience, 60 diffusion encoding directions and advanced tractography approaches (such as dRL) are required for reliable reconstruction of the imMFB, crucial factors to take into account when designing future studies.

Using constrained spherical deconvolution (CSD) (Jeurissen et al., 2011) for reconstructing the slMFB led to many false positive fibres projecting to the cortex. Similarly, when I used an angle threshold of 60 degrees I obtained overinclusive pathways (using both CSD and dRL). From my experience, the best results are obtained using an angle threshold of 45 degrees.

Initially I had tried to reconstruct the whole of the MFB (including both segments ventral and dorsal of the VTA), in line with the description of (Coenen et al., 2009).

However, following this approach, there is a spatial overlap with the superior cerebellar peduncle (SCP) which contains a proportion of slMFB fibres. Although this is anatomically correct, those segments may be less relevant for reward processing than the fibres emanating from the VTA. Therefore, for the purpose of my investigation (looking at the association between MFB microstructure and hedonic tone), I preferred to specifically reconstruct those segments of the MFB being localized dorsal of the VTA.

I have also tried to surround the SCP on a coronal plane and use it as an ñAND gateò since this approach may be more sensitive to reconstruct the imMFB (Figure 5.1). While this approach worked well for reconstructing the imMFB in many subjects, results seemed to be overinclusive regarding unwanted fibres stemming predominantly from the SCP. Interestingly, very recently this approach has been published by another group (Anthofer et al., 2015).

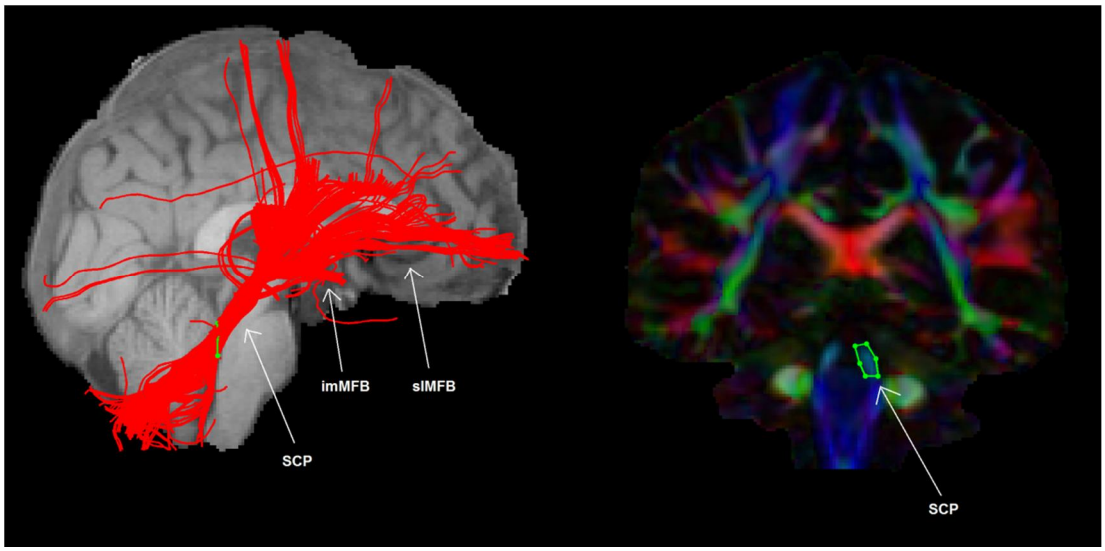

Figure 5.1 Alternative reconstruction of the MFB

A typical reconstruction of imMFB and slMFB based on a seed region surrounding the SCP is shown (using dRL and 60 diffusion encoding directions). In addition to the imMFB and the slMFB the SCP (that contains a proportion of imMFB and slMFB fibres) is being reconstructed.

Overall, the described algorithm of Chapter 2 provided the most reliable approach to specifically reconstruct fibres of the imMFB and slMFB that emerge from the VTA. By now this approach has already been used by different other researchers from our group in Cardiff and from my new group in Bern yielding prominent results (satisfactory reconstruction in about 90% out of approximately 200 data sets). Thus, the applied algorithm represents an important contribution to the existing tractography literature.

5.3 The role of neuroplasticity

Given that structural alterations of the slMFB seem to be dependent on clinical features of depression (e.g. melancholic, non-melancholic or remitted) results of Chapter 2 lead to the question whether neuroplastic changes occur during the time-span from depression to remission. I had the opportunity to analyze a longitudinal diffusion MRI data set in a group of 15 (11 unipolar, 4 bipolar) depressed patients once during a depressive episode and a second time during remission following successful antidepressive therapy. I have looked at the major limbic and reward system pathways: CB, UF, slMFB, PHC and fornix. Our data is suggestive of an age-dependent pattern of neuroplasticity within the CB and the PHC, while no changes were identified in the UF and in the slMFB. Thus, according to these results, microstructure of CB and PHC may serve as state markers while the microstructure of UF and slMFB may be trait markers of depression. However, in particular the absence of any neuroplastic changes within the slMFB contradicts our initial hypothesis. The absence of group differences may be due to substantial heterogeneity of the investigated group (in terms of depression severity, inclusion of bipolar and unipolar patients, differences in medication status, and differences in age). Although statistically controlling for these factors did not change the results, these factors may still have had an impact on the data. Further, only 4 out of the eleven patients with longitudinal data met criteria for melancholic depression, the subgroup where changes of the slMFB have been reported (Bracht et al., 2014).

5.4 The role of physical activity

The PHC where we identified changes in FA from depression to remission is not only relevant to reward processing but may also be influenced by physical activity. Reduced PA is one of the clinical features in depression and normalization of PA occurring from depression to remission can be commonly observed (Chapter 3). Thus, increases of PA may be directly related to clinical remission and to neuroplastic changes occurring during the time course from depression to remission. I specifically assessed the association between PA and white matter microstructure of the PHC and the fornix, the two main hippocampal pathways (Chapter 4). In this thesis I applied a further methodological novelty by acquiring and analyzing McDESPOT data enabling to estimate the myelin content of white matter pathways. Given the lack of specificity of DTI-derived measures this provides an

important step forward in white matter imaging. Our results are suggestive for a positive correlation between PA and myelination of the right PHC. Thus PA may contribute to reverse changes in white matter microstructure that are putatively present during depressive episodes. However, this causality can only be established applying a longitudinal study design. If this was to be true, this may also explain why depressed people generally tend to clinically improve if engaging in physical activity.

5.5 Work in progress and outlook

Participants recovering from depression investigated in my analyses of Chapter 3 included not only unipolar but also four bipolar depressed patients. However, so far it is not clear if any changes in FA can be observed in the slMFB in patients with bipolar disorder.

Consequently I am currently collaborating on the analyses of data sets in both bipolar depressed (collaboration in Bern) and bipolar remitted (collaboration in CUBRIC) patients and hope to address this question. Further, I am about to design a study to specifically investigate the longitudinal course of white matter microstructural changes of the slMFB in a group of severely (melancholic) depressed patients and in a group of moderately depressed participants.

In summary, future studies of white matter microstructure in depression should ideally investigate well characterized homogeneous subgroups, using a longitudinal study design and acquiring sixty diffusion encoding directions that enable the use of advanced tractography approaches. Further, novel sub-compartment specific imaging sequences such as McDESPOT may open exciting new insights in the neurobiology of depression.

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