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Review

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

Tobias Bracht [a,b,*], David Linden [a,c], Paul Keedwell [a]

[a] Cardiff University Brain Research Imaging Centre (CUBRIC), School of Psychology, Cardiff University, Cardiff, United Kingdom
[b] Translational Research Center, University Hospital of Psychiatry, University of Bern, Bolligenstrasse 111, 3000 Bern 60, Switzerland
[c] MRC Centre for Neuropsychiatry Genetics & Genomics, School of Medicine, Cardiff University, Cardiff, United Kingdom

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ABSTRACT

Background: 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 article to review literature on white matter microstructure alterations of the reward system in depression.
Method: We searched for 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. The relevant diffusion MRI literature was identified using PUBMED.
Results: Thirty-five studies were included. In people at familial risk for depression the main finding was reduced fractional anisotropy (FA) 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.
Limitations: Non-quantitative approach.
Conclusions: 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.
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* Corresponding author at: Translational Research Center, University Hospital of Psychiatry, University of Bern, Bolligenstrasse 111, 3000 Bern 60, Switzerland. Tel.: +41 31 930 9111; fax: +41 31 930 9404.
E-mail address: bracht@puk.unibe.ch (T. Bracht).

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1. Introduction

1.1. 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 (1954) who demonstrated that rats would work to induce electrical stimulation of specific brain regions. 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.

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., 2012; Der-Avakian and Markou, 2012; Walther et al., 2012), 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. 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 of 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., 2010; Bracht et al., 2014).

In this review we focus 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 Fig. 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., 2008). It has two branches, the infero-medial MFB (imMFB) and the slMFB. While the imMFB

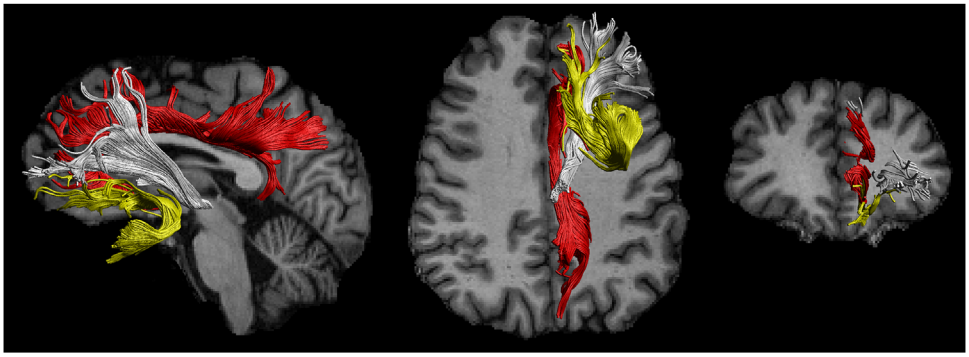

Fig. 1. Typical reconstructions for the cingulum bundle (red), the uncinate fasciculus (yellow) and the supero-lateral medial forebrain bundle (white) are shown. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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, 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, 2011; Panksepp, 2011).

1.3. Diffusion tensor imaging (DTI)

Diffusion tensor imaging (DTI) enables to indirectly draw conclusion on the underlying white matter tissue microstructure. If water diffuses freely in all directions this is called isotropic diffusion. However in 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 restricted diffusion which is described as anisotropic diffusion. The three dimensional diffusivity of water molecules can be modelled using DTI. Based on the eigenvalue and the eigenvector 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, 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).

1.4. 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 favour 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).

1.5. 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.

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

Table 1
Findings of tractography studies of the cingulum bundle, uncinate fasciculus and supero-lateral medial forebrain bundle 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.

At familial risk for depression		Adolescent depression		Adult depression	
Group differences	**No group differences**	**Group differences**	**No group differences**	**Group differences**	**No group differences**
Cingulum bundle					
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					
Huang et al. (2011)	Frodl et al. (2012), Keedwell et al. (2012)	Aghajani et al. (2014), 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					
		Bessette et al. (2014)		Bracht et al. (2014), Guo et al. (2012a 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)

family history. Furthermore, some studies have explored the influence of treatment-resistance and severity (Serafini et al., 2015). 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 review we separately discuss DTI findings in the core pathways of the reward system 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 they identified alterations in voxels, being localized along the anatomical course of CB, UF or slMFB.

2. Method

2.1. 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 MDD with healthy control subjects. We also included studies focusing on subjects at risk for developing MDD. We excluded studies of bipolar disorder and late life depression because these disorders differ in clinical presentation and presumably pathophysiology from major depression. Further, we excluded studies investigating depression as comorbidity of other disorders (e.g. AIDS, Parkinson's disease). Further exclusion criteria were comorbid substance abuse and neurological disorders (including mild cognitive impairment and dementia).

3. Results

A total of 35 publications were in included (for details of the included studies see Supplementary material). 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 indicating the presence or absence of group differences comparing diffusion properties (FA, MD, AD or RaD) between MDD-patients and healthy controls for the main reward system tracts: CB, UF and slMFB (Table 1, Fig. 1). In Table 1 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 (Fig. 1). We further include findings of VBA and TBSS studies being localized within the CB and the UF.

4. 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., 2014; 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, 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.

4.1. 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 the 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 cingulum bundles 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).

4.2. Uncinate fasciculus

In adolescents both increases (Aghajani et al., 2014) 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., 2014) 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 uncinate fasciculus 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.

4.3. 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 which 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, 2013). 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., 2012a; Korgaonkar et al., 2011; Peng et al., 2013; Tha et al., 2013; Walther et al., 2012; 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., 2012; Zhu et al., 2011; Zou et al., 2008) and treatment-resistant depression (de Diego-Adelino et al., 2014; Guo et al., 2012a; 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.

4.4. The effect of medication

Out of the 35 included studies in the review, 19 investigated unmedicated or treatment-naïve patients and have reported significant group differences. This strongly supports the assumption that identified brain changes of white matter in depression are associated with the disease process rather than being mere effects of medication. Bessette et al. (2014) compared medicated with unmedicated patients and found no group differences of FA between the two groups. De Diego-Adelino et al. (2014) controlled for medication effects which did not alter the results. Some of the tractography studies investigating medicated patients used comparison tracts or investigated multiple tracts and identified FA-changes localized in specific tracts which contradicts 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 antidepressive treatment may reverse changes of 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.

4.5. Implications of differences in methodological approaches

Six studies of 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, 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 investigated tracts (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 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.

4.6. Limitations

Firstly, we provide a selective overview of white matter changes in reward system pathways. 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 article to cover

these clinically very relevant issues. Secondly, owing to the small numbers of studies in most of the clinical subgroups, we do not provide a quantitative meta-analysis. It is a central goal of this review article 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, ROI and whole brain voxel-based approaches (TBSS and VBA), 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 diversity in applied methods, the sparse current literature of tractography studies in depression and differences in clinical populations it is currently not possible to conduct a meaningful meta-analysis of studies of the reward system. 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.

4.7. Summary and future directions

In this review, we have specifically 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., 2012a; 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 depression's 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, 2014; Keedwell et al., 2012; Walther et al., 2012).

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 "crossing fibres" 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., 2008) and may open exciting new possibilities for an in vivo assessment of specific neurobiological changes in depression.

Conflict of interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary materials

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2015.06.041.

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