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Depression severity is correlated to the integrity of white matter fiber tracts in late-onset major depression

Rikke Beese Dalby[a,*], Jesper Frandsen[b], M. Mallar Chakravarty[b,c], Jamila Ahdidan[a], Leif Sørensen[d], Raben Rosenberg[a], Poul Videbech[a], Leif Østergaard[b]

[a]Centre for Psychiatric Research, Aarhus University Hospital, Risskov, Skovagervej 2, DK-8240 Risskov, Denmark
[b]Center of Functionally Integrative Neuroscience (CFIN), Aarhus University Hospital, Aarhus, Denmark
[c]PET Center, Aarhus University Hospital, Aarhus, Denmark
[d]Department of Neuroradiology, Aarhus University Hospital, Aarhus, Denmark

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ABSTRACT

Cerebral white matter lesions (WMLs) are believed to play an important role in a subset of major depression (MD). We aimed to describe the impact of WMLs on white matter pathways in MD using diffusion tensor imaging (DTI) and magnetization transfer imaging. As a novel approach, we used DTI tractography to assess pathways intersected by WMLs. We examined 22 patients with late-onset MD and 22 age- and gender-matched controls. Parametric maps of fractional anisotropy (FA), apparent diffusion coefficient (ADC), and magnetization transfer ratio (MTR) were obtained to describe tissue integrity. The association between depression severity and the tract-specific localization of WMLs was analyzed on a voxel-by-voxel basis. We showed a significant positive association between depression severity and fiber tracts intersected by WMLs in the left superior longitudinal fasciculus and the right uncinate fasciculus. In both groups, WMLs had significantly lower FA and MTR, and higher ADC than both the tracts they intersected and the normal-appearing white matter (NAWM). In turn, the tracts intersected by WMLs had significantly lower FA and higher ADC than the NAWM. In conclusion, depression severity correlates with the tract-specific localization of WMLs. WMLs have a pronounced effect on white matter integrity in the pathways they intersect.
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1. Introduction

Imaging studies using T2-weighted magnetic resonance imaging (MRI) have reported an increased frequency of white matter hyperintensities, sometimes referred to as white matter lesions (WMLs), in major depression (MD), especially in late-onset and late-life MD (Herrmann et al., 2008; Videbech, 1997). As stated in the vascular depression hypothesis (Alexopoulos et al., 1997; Krishnan et al., 1997; Krishnan and McDonald, 1995), subcortical vascular changes may be an important contributor to WMLs, which in turn contribute to the pathogenesis in a subgroup of late-life MD by affecting mood-regulating neuronal pathways, either by single, localized lesions or by an accumulation of lesions exceeding a certain threshold (Alexopoulos et al., 1997). The presence of subcortical WMLs in late-life depression has been associated with cognitive impairment (Austin et al., 2001; Goodwin, 1997; Herrmann et al., 2007), functional impairment (Steffens et al., 2002), poor treatment outcome (Alexopoulos et al., 2002, 2008; Chen et al., 2006; Hickie et al., 1995, 1997; Iosifescu et al., 2006; O'Brien et al., 1998; Simpson et al., 1998; Steffens et al., 2001; Taylor et al., 2003b), and a greater risk of subsequent dementia (Steffens et al., 2007). Although reports in the depression literature have found the WMLs to be mainly located in fronto-striatal circuits (Greenwald et al., 1998; MacFall et al., 2001; O'Brien et al., 2006; Sheline et al., 2008; Taylor et al., 2003a; Videbech et al., 2004), and in the basal ganglia (Videbech, 1997), the relation between lesion characteristics, their interference with specific white matter pathways, severity of symptoms, and disease remains largely unknown.

Recent advances in MRI technology, such as diffusion tensor imaging (DTI) and magnetization transfer imaging have facilitated the study of microstructural changes in neuropsychiatry. Magnetization transfer (MT) imaging is sensitive to water bound to macromolecules and has been demonstrated in post mortem studies to correlate with myelin content and axonal density (Chen et al., 2007; van Waesberghe et al., 1999). The method, quantified by the magnetization transfer ratio (MTR), which is a compound index of the exchange between free and protein-bound water protons pools, is regarded as superior to conventional MRI with respect to the detection and quantification of subtle white matter changes, e.g. in multiple sclerosis (Tofts et al., 2003). Studies using MT imaging in depression have revealed lower MTR in multiple white matter regions, including the fronto-striatal and limbic regions, and the genu and splenium of the corpus callosum (Gunning-Dixon et al., 2008; Kumar et al., 2004).

* Corresponding author. Tel.: +45 7789 3608; fax: +45 7789 3619.
E-mail address: rbdalby@dadlnet.dk (R.B. Dalby).

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DTI is based on the random thermal diffusion of water molecules (Basser et al., 1994; Pierpaoli et al., 1996) and is highly sensitive to changes in tissue microstructure, such as axonal injury (e.g. demyelination) and intracellular or extracellular edema, which may not be visualized with conventional MRI. Water diffusion is restricted by barriers such as cell membranes and myelin, which introduces a directional dependence termed *anisotropy*, quantified by means of an FA index (Beaulieu, 2009). The apparent diffusion coefficient (ADC) measures the magnitude of diffusion. DTI studies in MD have shown reduced FA in several white matter regions, primarily the prefrontal white matter regions, such as the superior frontal gyrus and anterior cingulate cortex (ACC), and in temporal regions, in elderly depressed subjects compared with controls (Bae et al., 2006; Nobuhara et al., 2006; Taylor et al., 2004; Yang et al., 2007). In general, DTI studies of affective disorders consistently identify reduced anisotropy in the frontal and temporal lobes and tracts of subjects with affective disorders relative to control subjects (Sexton et al., 2009). In remitted geriatric depression others have found the FA reductions to be more widespread and also to include the parietal and occipital regions as well as the basal ganglia (Yuan et al., 2007). In addition, changes in FA in distributed cerebral networks have been associated with failure to remit in geriatric depression (Alexopoulos et al., 2008; Taylor et al., 2008).

During the last decade, advances in DTI have facilitated the study of tract-specific measures of cerebral microstructural integrity *in vivo*, a technique known as tractography or fiber tracking (Basser et al., 2000) — see, for example, the review by Mori and van Zijl (2002). DTI tractography combines measurements of water diffusion direction in each image voxel to reconstruct the trajectory of fiber pathways, thus reflecting neural connectivity (Basser et al., 2000). The method has enabled virtual "dissections" of major white matter fascicles in the living brain (e.g., see Catani et al., 2002). Application of DTI tractography in depression has mainly been to define and describe anatomical connectivity in well-defined regions of interest, such as targets of deep brain stimulation (Gutman et al., 2009; Johansen-Berg et al., 2008).

We have previously reported on WMLs and vascular risk factors in late-onset MD (Dalby et al., 2010). In this study, we present a novel approach to examine the impact of WMLs on gray matter connectivity by using DTI tractography to reveal the pathways potentially affected by WMLs. To our knowledge, DTI tractography has not previously been implemented to assess the anatomical extent and impact of WMLs on white matter integrity, which we present here. The aim of our study was to combine tractography and measures of white matter integrity to determine the tract-specific localization of WMLs, and to characterize the WMLs as well as the tracts they intersect in patients with late-onset MD compared with non-depressed, age- and gender-matched controls. Specifically, we hypothesized that in late-onset MD: 1) WMLs co-locate with mood-regulating pathways to a higher extent in patients than in non-depressed controls, that 2) depression severity is associated with WMLs intersecting mood-regulating pathways, that 3) WMLs show impaired white matter integrity compared with the surrounding white matter, and that 4) fiber tracts intersected by WMLs show impaired white matter integrity compared with the surrounding white matter.

2. Materials and methods

2.1. Subjects

Whole-brain MRI data were acquired from 22 patients with late-onset, first-episode MD and 22 controls with no history of psychiatric illness. The two groups were matched for age and gender. A brief account of the clinical and socio-demographic data is given in Table 1. The patients were consecutively recruited from psychiatric hospitals in the County of Aarhus through referral to the Neuropsychiatric Clinic, Aarhus University Hospital, Risskov, Denmark, and from outpatient psychiatric clinics in the County of Aarhus, Denmark. All patients met the DSM-IV (American Psychiatric Association, 2000) criteria for major depression and the ICD-10 criteria (World Health Organization, 1993) for moderate to severe depression within 4 weeks of inclusion. Late onset was predefined as first onset of depressive symptoms after the age of 50 years. Controls were recruited through advertisement in local papers and went through a preliminary sorting for exclusion criteria (see below) in a thorough telephone screening procedure. At the inclusion all subjects were assessed with selected parts of the SCAN structured interview (Wing et al., 1998) and were rated for severity of depressive symptoms with the Bech–Rafaelsen Melancholia Scale (MES) (Bech, 2002), which is an extended version of the 6-item Hamilton Depression Scale. The patients underwent a clinical neuropsychological examination or alternatively the Mini-Mental State Examination (MMSE) test (Folstein et al., 1975), depending on clinical and practical circumstances (results not shown). All controls were screened with the MMSE test. Both patients and controls were thoroughly interviewed about their medical history and were screened for concurrent medical diseases and alcohol abuse by standard blood tests, including thyroid function, and they all underwent a neurological exam. According to the Edinburgh Handedness Inventory (Oldfield, 1971), all included subjects were right-handed, except for three patients and one control who were ambidextrous. Current medication and information on vascular risk factors, such as hypertension and smoking, was carefully recorded (Dalby et al., 2010), and a composite vascular risk score was calculated as defined in the Framingham Study (Wolf et al., 1991). Exclusion criteria for both groups were organic brain disease (e.g. former stroke, cerebral vascular malformations, or epilepsy), former brain injury, substance dependency, and conventional contraindications to undergo MRI scanning. Written informed consent was obtained from all study subjects, and the study was approved by the regional ethics committee on research and in accordance with the Declaration of Helsinki (World Medical Association, 2008).

Table 1
Socio-demographic and clinical characteristics of patients with late-onset major depression and non-depressed controls. MES = Bech–Rafaelsen Melancholia Scale.

	Patients ($n=22$)		Controls ($n=22$)		Statistics	
	Mean	S.D.	Mean	S.D.	z	P
Age (years)	57.4	4.6	59.2	7.3	0.5	0.64
Vascular risk factor score[a]	6.9	4.7	6.8	4.4	0.05	0.96
MES score	16.5	5.8	0.3	0.8	−5.9	<0.001[b]
	n	%	n	%		P
Gender						1.00
Male	7	31.8	7	31.8		–
Female	15	68.2	15	68.2		–

[a] Composite vascular risk factor score as described in the Framingham Study (Wolf et al., 1991), comprising age, systolic blood pressure, antihypertensive treatment, diabetes, cigarette smoking, cardiovascular disease (coronary heart disease, cardiac failure, or intermittent claudication), atrial fibrillation, and left ventricular hypertrophia.
[b] Significant results at $P<0.05$.

2.2. Scan protocol

MRI scans were obtained with a whole-body 3T GE Signa HDx scanner (GE Medical Systems, Milwaukee, WI, USA). The MRI protocol consisted of an axial fast spoiled gradient echo (FSPGR) 3D T1-weighted sequence (TE = 2.84 ms, TR = 6.64 ms, TI = 750 ms, flip angle = 14, field of view (FOV) = 240 mm, matrix 256 × 256, slice thickness = 1.2 mm, no gap), an axial T2-weighted fluid-attenuated inversion recovery (FLAIR) sequence (TE = 120 ms, TR = 8650 ms, TI = 2250 ms, FOV = 240 mm, matrix 224 × 256, slice thickness = 5 mm, gap = 1.5 mm), an axial T2-weighted sequence (TE = 112 ms, TR = 5400 ms, field of view =

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