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Association of microstructural white matter abnormalities with cognitive dysfunction in geriatric patients with major depression

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ABSTRACT

Major depression disorder (MDD) is one of the most common causes of disability in people over 60 years of age. Previous studies have linked affective and cognitive symptoms of MDD to white matter (WM) disruption in limbic-cortical circuits. However, the relationship between clinical cognitive deficits and loss of integrity in particular WM tracts is poorly understood. Fractional anisotropy (FA) as a measure of WM integrity was investigated in 17 elderly MDD subjects in comparison with 18 age-matched controls using tract-based spatial statistics (TBSS) and correlated with clinical and cognitive parameters. MDD patients revealed significantly reduced FA in the right posterior cingulate cluster (PCC) compared with controls. FA in the right PCC (but not in the left PCC) showed a significant positive correlation with performance in a verbal naming task, and showed a non-significant trend toward a correlation with verbal fluency and episodic memory performance. In control subjects, no correlations were found between cognitive tasks and FA values either in the right or left PCC. Results provide additional evidence supporting the neuronal disconnection hypothesis in MDD and suggest that cognitive deficits are related to the loss of integrity in WM tracts associated with the disorder.

1. Introduction

Major depression disorder (MDD) is a chronic disease with a prevalence rate of 6.5–9% in people over 60 years of age and is considered one of the most important causes of disability (Greenberg et al., 1993; Lyness et al., 2002). Along with mood alterations, cognitive symptoms are present in a substantial proportion of MDD patients (Lesser et al., 1996; Alexopoulos et al., 2008a) and can be a persistent symptom even after effective treatment of a depressive episode (Elderkin-Thompson et al., 2006). Previous investigations suggest that executive dysfunction is associated with lower response to antidepressant therapy (Alexopoulos et al., 2008b), and longitudinal studies estimate that 13–20% of those with moderate to severe MDD develop mild cognitive impairment within a period of 3–6 years (Barnes et al., 2006; Geda et al., 2006). In addition to executive dysfunction a variety of other cognitive skills related to executive control may be affected, such as set-shifting, processing speed, episodic memory and verbal fluency (Herrmann et al., 2007).

Genetic (Taylor et al., 2005), neuropathological (Thomas et al., 2002) and functional magnetic resonance imaging studies (Bae et al., 2006; Drevets, 2007) have suggested that MDD results from system-level disorder that affects functionally integrated pathways involving limbic, subcortical and cortical areas. Functional and pathological studies are supported by structural magnetic resonance imaging (MRI) results showing brain volumetric reductions in the frontal cortices, amygdala, hippocampus and cingulate regions of depressed patients (Bae et al., 2006; Koolschijn et al., 2009). These anatomical regions are interconnected by a few major white matter tracts such as the cingulum bundle, the fornix and the uncinate fasciculus (Schermuly et al., 2010). These results support the limbic-cortical network dysfunction model proposed to describe the biological underpinnings of MDD (Mayberg, 2003). In the last decade an increasing number of MRI studies with depressed patients have applied diffusion tensor imaging (DTI) to investigate the role of specific white matter (WM) tracts in the limbic-cortical networks (Sexton et al., 2009). One of the most common indices of DTI to assess the WM structural organization is fractional anisotropy (FA), a scalar measure ranging from 0 to 1 that rates the degree of anisotropy in diffusion (Gupta et al., 2006). Because of its properties, particularly the possibility of revealing

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microstructural changes in cerebral networks associated with MDD (Murphy et al., 2007), DTI is an important tool for investigating age-related affective disorders (Burzynska et al., 2010).

DTI findings observed that depression can accelerate the loss of WM integrity (Shimony et al., 2009) and that increasing WM abnormalities were found are related to limbic and dorsal cortical communication in geriatric MDD (Tekin and Cummings, 2002; Rogers et al., 2004; Alexopoulos et al., 2008a). To date relatively few studies have examined the relation between WM integrity and cognitive dysfunction in depression, and existing evidence indicates an association of low FA with deficits in response inhibition (Murphy et al., 2007), executive control (Yuan et al., 2007), and processing speed (Shimony et al., 2009).

Most of the earlier DTI studies in MDD used a region-of-interest (ROI) approach, with brain areas being delineated manually or with semi-automated methods (Alexopoulos et al., 2002; Nobuhara et al., 2004; Taylor et al., 2004; Bae et al., 2006). However, the ROI approach has been criticized in the recent literature (Sexton et al., 2009; Stricker et al., 2009; Zhu et al., 2011), namely because of the difficulty in precisely replicating ROIs, difficulties in the anatomical delineation of the ROI, and use of pre-selected brain regions rather than considering diffusion changes in the whole brain. To improve the objectivity and interpretability of DTI studies, the technique of tract-based spatial statistics (TBSS) was developed to enable DTI scans to be compared across subjects more robustly (Smith et al., 2006); furthermore, TBSS reduces the problem of misalignment (Snook et al., 2007) and is based on voxelwise analysis, which approaches the whole brain without any a priori selection of regions. Therefore, TBSS is a promising approach to identify more accurately anatomical changes in MDD throughout the WM structure. TBSS results may have important repercussions for clinical practice, as they can help in developing biomarkers for the diagnosis and treatment based on diffusivity changes across time in specific brain networks of MDD (Alexopoulos et al., 2002).

In the current study, we investigated WM microstructural integrity in a sample of non-demented elderly individuals with MDD in comparison with age-matched healthy controls. Our objectives were twofold: 1) to investigate WM abnormalities in the MDD group using TBSS; and 2) to examine if cognitive performance in MDD was associated with global and regional WM abnormalities, particularly in the tracts that have previously been identified as compromised in MDD.

We expected to identify decreased anisotropy in the MDD group in comparison with non-depressed subjects, specifically in the major WM tracts connecting limbic-cortical circuits. It was also hypothesized that cognitive deficits in MDD subjects would be correlated with reduced FA in these WM tracts, as a component of disrupted connectivity in depression.

2. Materials and methods

2.1. Clinical assessment

All subjects ($n=40$) were examined by two members of the Department of Psychiatry (FF and TK) with experience in Geriatric Psychiatry. Medical assessment was based on the Structured Clinical Interview for DSM-IV (SCID) (American Psychiatric Association, 1994) for major depression in the patient group and lifetime absence of psychiatric illness in the control group. The entire cohort was screened to exclude mild cognitive impairment or dementia using the Petersen criteria (Petersen, 2004) and DSM-IV, respectively. All subjects included in the study had Clinical Dementia Rating Scale (Hughes et al., 1982) scores of 0. All individuals were evaluated with the Hamilton Depression Rating Scale (HAMD; Hamilton, 1960), a 21-item rating scale, and with a shorter version of the Geriatric Depression Scale (GDS) with 15 items (Sheikh and Yesavage, 1986).

Exclusion criteria for all participants were a history of seizures, psychotic symptoms, neurological diseases, dementia, impaired thyroid function, abuse of alcohol or substance abuse or dependence. The study protocol was prepared in accordance with ethical standards laid down in the declaration of Helsinki and was approved by the local ethics committee. Patients and controls signed a written consent following a full oral description of the study.

2.2. Neuropsychological assessment

For neuropsychological assessment, a test battery was used to examine several cognitive domains: executive function, episodic memory, working memory, attention, verbal fluency, visual constructional praxis and language skills. In addition to the Mini-Mental State Examination (MMSE; Folstein et al., 1975), all participants were assessed with the battery of the Consortium to Establish a Registry for Alzheimer's Disease — CERAD (Morris et al., 1989). Specific CERAD subtests included verbal fluency (semantic category), constructional praxis (figure copying), language (a reduced version from the Boston Naming Test — BNT) and episodic memory (word list learning, delayed free recall and word recognition). Visual memory and working memory were assessed by recall of geometric figures presented earlier in the CERAD test. The Trail Making Test (TMT), which evaluates psychomotor speed (TMT A) and executive function (TMT B) (Reitan, 1958) was also included.

For statistical analysis, raw scores from the following cognitive variables were taken from CERAD tests: immediate recall for words (sum of lists 1, 2 and 3), figure copying (circle, triangle, rhombus, rectangle, cube); and delayed recall for words and for visual memory (geometric figures). Raw scores (time in seconds) were also taken from TMT A and B and Verbal Fluency (number of animals and words).

As most variables were not normally distributed, non-parametric tests were used. Two-tailed correlations and independent group comparisons were performed with Spearman's rank correlation and the Mann–Whitney-*U* test, respectively. In order to control for the effects of education on cognitive tasks, analysis of covariance (ANCOVA) was employed. A p value <0.05 was adopted as statistically significant. All statistical analyses were performed with SPSS version 15.0.

2.3. MRI data acquisition

Imaging was performed on a 3-T MRI scanner (Trio, Siemens Medical Solutions, Erlangen, Germany). DTI scans were acquired using a gradient echo sequence with the following parameters: repetition time (TR) = 8200 ms, echo time (TE) = 99 ms, acquisition voxel size = $2\times2\times2$ mm^3, 60 transaxial slices, 60 diffusion encoding directions (b = 1000 s/mm^2), slice thickness = 2 mm, field of view = 192 mm, acquisition matrix = 96×96; total acquisition time: 9 min 42 s. Ten images with no diffusion gradient (B0) were acquired. We allowed for parallel acquisition of independently reconstructed images using generalized auto-calibrating partially parallel acquisitions [GRAPPA (Griswold et al., 2002)]. For each subject a total of three consecutive DTI scans were acquired.

2.4. Control for white matter lesions

A fluid attenuated inversion recovery sequence (FLAIR) was conducted to identify subjects with WM lesions, using the following parameters: TR = 10000 ms; TE = 105 ms, $1\times1\times3$ mm^3, 38 slices. All FLAIR images were visually inspected by one investigator (CK) blind to any clinical data. In order to exclude patients with macrostructural subcortical vascular disease, the severity of WM lesions was estimated using the Fazekas scale (Fazekas et al., 1987), and the parameters of WM volume estimation of the LADIS study (Inzitari et al., 2009). Five subjects with severe WM lesions (>20 mm diameter and grade = 3) were excluded.

2.5. Demographic and clinical characteristics of the sample

A total of 35 subjects remained for further analysis, as shown by Table 1. The two groups comprised 17 patients diagnosed with a MDD (8 females, mean age = 65.5, S.D. = 5.5; range = 59–78 years) and 18 subjects (11 females, mean age = 66.4, S.D. = 3.5, range = 61–74 years) assessed as a control group. Depressed patients and controls did not differ in gender, age or subcortical vascular lesions, but did differ in years of education (Table 1). Twelve (70.58%) patients were currently receiving antidepressant therapy. The remaining patients ($n=5$, 29.42%) had their first depressive episode and were drug naive at the time of measurement. Four patients (23.52%) received co-therapy with antipsychotics and four with (23.52%) low-dose benzodiazepines, mainly prescribed for sedation. One patient had augmentation of selective serotonin reuptake inhibitor (SSRI) treatment with lithium; none of the patients had received electroconvulsive therapy. Mean age of disease onset was 46.88 (S.D. = 14.53) years.

2.6. DTI preprocessing

DTI processing and voxelwise statistical analysis were performed using tools from the Oxford Centre for Functional MRI of the Brain — FMRIB free software library (FSL — http://www.fmrib.ox.ac.uk/fsl/). The three DTI datasets acquired for each subject were first merged into a single volume. Motion and eddy current correction, as well as an affine registration to the reference volume (b0), were then performed (Jenkinson and Smith, 2001). The volumes of each of the three scans were extracted from the merged image providing three motion and eddy current corrected datasets which were averaged to produce a single DTI image. FSL's Brain Extraction Tool (BET) (Smith, 2002) was applied to the averaged DTI image, and a DTI model, including maps of FA using the FMRIB Diffusion Toolbox. The preprocessing steps were performed automatically using an in-house script pipeline (MR Imaging and Spectroscopy Toolbox, Institute of Neuroradiology, University Hospital, Frankfurt/Main, Germany).