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Correlations between Stroop task performance and white matter lesion measures in late-onset major depression

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

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

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ABSTRACT

Cerebral white matter lesions (WMLs) are believed to play an important role in a subset of patients with late-onset depression by affecting the white matter connectivity in circuitries essential for mood and cognition. In this study we used diffusion tensor imaging-based (DTI-based) tractography to assess white matter fiber tracts affected by deep WMLs (DWMLs) in patients with late-onset major depression and age- and gender-matched controls. Tractography outcome, illustrated as pathways affected by DWMLs, was analyzed for associations with cognitive performance on the Stroop Test (ST). The patients ($n=17$) performed significantly worse on the ST than the controls ($n=22$). Poor performance on the ST correlated with higher lesion load. Regression analysis showed a significant correlation between poor performance on the ST and tracts affected by DWMLs in multiple brain areas in the control group, but very sparse correlation in the patient group. Our results suggest that DWMLs play an important role in the cognitive performance of controls,whereas their influence in depressed patients is overruled by additional, state-dependent factors. Future focus on the tract-specific localization of WMLs using DTI tractography may reveal important associations between neuroconnectivity and clinical measures.

1. Introduction

Depression is a heterogeneous disease with a large degree of medical co-morbidity (Evans et al., 2005). Increasing evidence suggests that cerebrovascular disease may be an important factor in the pathogenesis of a subtype of late-onset depression termed *vascular depression* (Alexopoulos et al., 1997a; Krishnan et al., 1997). The prevailing view is that vascular disease, in particular small-vessel disease, predisposes to depression through ischemic white matter changes, such as white matter lesions (WMLs), which are believed to disrupt or impair the white matter fiber structure in circuitries essential for mood and cognition (Alexopoulos et al., 1997a; Krishnan et al., 1997). WMLs appear as white matter hyperintensities on T2-weighted magnetic resonance imaging (MRI) of the brain and are commonly said to reflect various degrees of ischemic tissue damage ranging from mild perivascular alterations to gliosis, variable loss of fibers, and rarefaction of myelination (Fazekas et al., 1993; Pantoni and Garcia, 1997; Thomas et al., 2002; 2003). Although WMLs are a common finding in healthy elderly individuals, imaging studies using MRI have reported an increased frequency of WMLs in depression (Videbech, 1997), especially in late-onset depression (Herrmann et al., 2008). The lesions are mainly situated in subcortical regions and their frontal white matter projections (Greenwald et al., 1998; MacFall et al., 2001; Taylor et al., 2003; Videbech et al., 2004; O'Brien et al., 2006; Sheline et al., 2008; Dalby et al., 2010a; Mueller et al., 2010), and in the basal ganglia (Videbech, 1997).

White matter abnormalities such as WMLs have been associated with impaired cognitive performance, including deficits in executive function, in both normal aging (de Groot et al., 2000; Gunning-Dixon and Raz, 2000; Rabbitt et al., 2007; Vannorsdall et al., 2009) and depression (Goodwin, 1997; Austin et al., 2001; Herrmann et al., 2007). Severe WMLs, especially deep WMLs (DWMLs), have been suggested as a predictor of greater deficits in executive functions in late-life depression (Kohler et al., 2010).

Cognitive deficits related to late-onset depression mainly comprise reductions in processing speed and executive function (Herrmann et al., 2007), the latter covering a variety of cerebral processes, which are responsible for planning, cognitive flexibility, abstract thinking, initiating appropriate actions, and selecting relevant sensory information. A widely used neuropsychological test of executive function is the Stroop Test (ST) (Stroop, 1935). The basic principle of the test is to create

* Corresponding author at: Centre for Psychiatric Research, Aarhus University Hospital, Risskov, Skovagervej 2, DK-8240 Risskov, Denmark. Tel.: +45 7847 1142; fax: +45 7847 1108.
E-mail address: rbdalby@dadlnet.dk (R.B. Dalby).

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interference between word reading and color naming, i.e. when a subject must name the color of a word which spells the name of a different color, thus creating interference between automatic and effortful information processing. In general, performance on the ST has been viewed as a sensitive, but not specific, indicator of prefrontal function, including processing speed and attentional control. The interference part of the test, in particular, is regarded as a measure of response inhibition, which is considered part of our executive control (MacLeod, 1991; Alvarez and Emory, 2006). Recent studies have correlated poor performance on the ST with an increased burden of WMLs in depression (Videbech et al., 2004; Sheline et al., 2008), suggesting that WMLs have a functional impact on neural circuitries underlying cognitive tasks, in consistency with the vascular depression hypothesis (Alexopoulos et al., 1997a; Krishnan et al., 1997) as well as the classic theories of disconnection syndromes (Catani and ffytche, 2005). In addition, the presence and severity of subcortical WMLs has been linked to psychomotor retardation (Simpson et al., 2000), which is frequently observed in late-onset depression (Alexopoulos et al., 1997b).

In spite of the increasing evidence towards WMLs playing a major role in late-onset/late-life depression, the exact anatomical and functional impact of WMLs on white matter integrity remains incompletely defined. In a recent review, Galluzzi et al. (Galluzzi et al., 2008) suggest that WMLs might affect brain function through impairment of brain plasticity and reserve. During the last decade, advances in MRI, such as diffusion tensor imaging (DTI), have facilitated the study of the microstructural integrity of brain tissues *in vivo* and the reconstruction of white matter trajectories, a technique known as *tractography* (Basser et al., 2000; Mori and van Zijl, 2002). DTI is based on the measurement of the random diffusion of water molecules in tissue (Basser et al., 1994; Pierpaoli et al., 1996), commonly described by fractional anisotropy (FA), and tractography combines the knowledge on water diffusion size and direction in each image voxel to reconstruct a fiber pathway, thus reflecting axonal connectivity (Basser et al., 2000).

The presumed mechanism whereby WMLs are associated with cognitive dysfunction involves various degrees of disruption or even disconnection of white matter circuits. We recently introduced a novel method of MRI tractography to describe the localization and impact of DWMLs on white matter structure (Dalby et al., 2010b), thereby focusing on the tract-specific localization of the lesions, which cannot be visualized with conventional MRI. We showed that DWMLs profoundly affect white matter integrity, measured by diffusion and magnetization transfer parameters, both within the lesion sites themselves and along the neuronal pathways they intersect, and do so in a similar manner in patients with late-onset major depression and controls (Dalby et al., 2010b). The aim of the present study was to use DTI tractography to examine the extent to which white matter fiber tracts affected by DWMLs are associated with cognitive deficits and psychomotor retardation in late-onset major depression compared with controls.

2. Methods

2.1. Subjects

Twenty-two patients with late-onset, first episode major depression and 22 controls, matched for age and gender and with no history of psychiatric illness, underwent whole-brain MRI. The patients were consecutively recruited from the Neuropsychiatric Clinic, Aarhus University Hospital, Risskov, Denmark, and comprised in-patients at psychiatric hospitals and out-patients from psychiatric clinics in the County of Aarhus, Denmark. Controls were recruited through advertisement in local papers. 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 the onset of depressive symptoms after the age of 50 years. All subjects were assessed with selected parts of the SCAN structured interview (Wing et al., 1998) at study entry, including screening questions to exclude mania/hypomania (chapter 10) and psychotic symptoms (chapter 14). The interview addressed both the present state (within 4 weeks of examination) and past life, the latter to exclude any prior psychiatric history. The patients underwent a comprehensive neuropsychological examination program (results not shown), including the ST (see below). The controls were screened with the Mini-Mental State Examination (MMSE) test (Folstein et al., 1975) and also completed the ST. Depression severity was rated with the Bech-Rafaelsen Melancholia Scale (MES) (Bech, 2002) at the inclusion. 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. All subjects were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971), except for three patients and one control who were ambidextrous. Current medication and information on vascular risk factors, such as hypertension and smoking, were carefully recorded (Dalby et al., 2010a). Exclusion criteria for both groups were organic brain disease (e.g. former stroke, cerebral vascular malformations, epilepsy, or other known neurological diseases), former brain injury, and conventional contraindications to undergo MRI scanning. Exclusion criteria also included any lifetime psychiatric comorbidity caused by alcohol or psychoactive drugs, including substance dependency or substance abuse, defined according to the ICD-10 or DSM-IV. 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.

2.2. Stroop Test (ST)

Subjects were tested with the Golden version of the ST (Golden and Freshwater, 2002), which consists of the following three parts: (I) a word part where the subject has to read aloud color names printed in black, (II) a color part where the subject has to name the ink color of printed X's, and (III) a color-word part where the subject has to name the ink color of a printed word that spells the name of a different color. The test yields three scores (C = color, W = word, and CW = color-word) based on the number of correctly read or named items in 45 s in the three parts. An interference score can be calculated on the basis of the performance by the Golden formula (Golden and Freshwater, 2002):

$$interference\ score = CW\ score - predicted\ CW\ score,$$

where the predicted CW score is = (W*C)/(W + C). The interference score is regarded as a measure of executive functions, including selective attention and response inhibition (Goldberg and Bougakov, 2005; Alvarez and Emory, 2006). A low Golden interference score reflects a lower CW score than predicted, i.e. a higher degree of interference, and thus a lower task performance.

2.3. Psychomotor retardation

Since performance on the ST may be influenced by psychomotor slowing (Degl'Innocenti et al., 1998; Lemelin and Baruch, 1998), all subjects were additionally rated with the Widlöcher Depressive Retardation Scale (WDRS) (Widlöcher, 1983). The WDRS score refers to paucity of movements, retarded speech, paucity of thought, lack of reactivity, and difficulty of initiation.

2.4. MRI protocol and image analysis

MRI scans were obtained with a whole-body 3 Tesla 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 (TI = 750 ms, flip angle = 14, field of view = 240 mm, matrix 256*256, slice thickness = 1.2 mm, no gap), an axial T2-weighted fluid-attenuated inversion recovery (FLAIR) sequence (TE1 = 120 ms, TR = 8650 ms, TI = 2250 ms, field of view = 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 = 240 mm, matrix 416*416, slice thickness = 5 mm, gap = 1.5 mm), and an axial DTI sequence (TE1 = minimum, TR = 12500, flip angle = 14, field of view = 240 mm, matrix 128*128, slice thickness = 3.5 mm, no gap). The DTI scan was performed using double spin echo single shot echoplanar imaging with 26 gradient directions (b = 1000 s/mm^2) and 6 b = 0 acquisitions. We used a birdcage head coil along with restraining foam pads to minimize the head motion.

The T1-weighted images were non-linearly transformed to match the MNI standard brain (Evans et al., 1994; Mazziotta et al., 2001). The subject-to-MNI space transformation was estimated using the ANIMAL algorithm (Collins et al., 1995; Robbins et al., 2004).

2.5. White matter lesions

DWMLs were identified simultaneously as hyperintensities on the T2-weighted and FLAIR images by an experienced neuroradiologist (author LS), blinded to subject status. The DWMLs were manually labeled (author RBD) on the FLAIR images using Display software (McConnell Brain Imaging Centre, MNI, McGill University, Montreal, Quebec, Canada). The labeling was performed for all subjects in random order and was completed in a single batch after the last inclusion of subjects. Initial labelings were repeated to ensure uniformity through the procedure. We used a single rater to avoid inter-rater variability. We did not test for intra-rater reliability. The labeled lesions for each subject were resampled to a binary lesion mask in native space, each voxel presenting a value of 0 (= no lesion) or 1 (= lesion). Based on previous studies reporting distinct neuropathological (Fazekas et al., 1993; Thomas et al., 2002; 2003) as well as functional differences (Kim et al., 2008) between DWMLs and periventricular WMLs (PVLs), and a stronger association between DWMLs and depression (Krishnan et al., 2006), especially