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Frontal white matter integrity in adults with Down syndrome with and without dementia

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ABSTRACT

Adults with Down syndrome (DS) are at high risk for developing Alzheimer's disease after the age of 40 years. To detect white matter (WM) changes in the brain linked to dementia, fractional anisotropy (FA) from diffusion tensor imaging was used. We hypothesized that adults with DS without dementia (DS n = 10), DS with dementia (DSAD n = 10) and age matched non-DS subjects (CTL n = 10) would show differential levels of FA and an association with scores from the Brief Praxis Test and the Severe Impairment Battery. WM integrity differences in DS compared with CTL were found predominantly in the frontal lobes. Across all DS adults, poorer Brief Praxis Test performance correlated with reduced FA in the corpus callosum as well as several association tracts, primarily within frontoparietal regions. Our results demonstrate significantly lower WM integrity in DS compared with controls, particularly in the frontal tracts. DS-related WM integrity reductions in a number of tracts were associated with poorer cognition. These preliminary results suggest that late myelinating frontal pathways may be vulnerable to aging in DS.

1. Introduction

The most common cause of Down syndrome (DS) is triplication of chromosome 21, resulting in a phenotype that is accompanied by altered brain development and other neurologic features (Lott, 2012). However, a key challenge for adults with DS as they age is the increasing risk for developing Alzheimer's disease (AD). Despite estimated ages of dementia onset in DS of 48–56 years (reviewed in Head et al., 2007; Schupf and Sergievsky, 2002), AD neuropathology appears in virtually all adults with trisomy 21 after the age of 40 years (Wisniewski et al., 1985). Thus, there may be up to a 10-year delay in the onset of clinical symptoms of dementia and the presence of AD neuropathology, as has been suggested for late onset sporadic AD in the general population.

Diffusion tensor imaging (DTI) represents a noninvasive in vivo method for characterizing the microstructural properties of white matter (WM) by measuring the rate and direction of diffusion of water molecules in the neural tissue (Basser et al., 2000) that can occur equally (isotropic) or unequally (anisotropic) in all directions. Anisotropy in WM indicates disruption in WM integrity resulting from a loss of compactness of WM tracts, their myelination, and/or number of axons within the tract studied (Wimberger et al., 1995). Fractional anisotropy (FA) measures these changes in ranges from 0 (diffusion that is equal in all directions representing poor white matter integrity) to 1 (diffusion that is predominately in one direction representing good white matter integrity) (Pfefferbaum and Sullivan, 2003).

DTI has been used extensively to study both brain aging and disease states such as AD (Sexton et al., 2011). Results from several studies have suggested that FA decreases are associated

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with age-related declines on memory and executive control tasks (Bucur et al., 2008; Gold et al., 2010a, 2010b). Studies of normal aging have consistently reported decreases in FA, suggesting a loss in WM integrity inherent in the aging process, that is amplified in disease states such as AD (Madden et al., 2012). Most DTI studies of aging and dementia have reported that age-related FA declines follow an anterior-posterior gradient with WM in frontal regions showing the earliest and largest declines are associated with executive decline evident on neuropsychological testing (Madden et al., 2009).

In DS, there is a growing literature suggesting that the earliest manifestations of dementia appear to involve changes in personality and behavior (Aylward et al., 1997; Cooper and Prasher, 1998; Holland et al., 2000), which are likely frontal-dependent. Pragnosia or socially deficient communication may also be an early sign of frontal lobe dysfunction in DS and may represent a striking change from previous well-developed social capacities in the disorder (Nelson et al., 1995). Thus, executive dysfunction may be an early sign of aging and progression to dementia in DS. There are several studies describing magnetic resonance structural and/or volumetric differences and changes with age and dementia in DS (Beacher et al., 2009; Krasuski et al., 2002; Pinter et al., 2001; Roth et al., 1996; Teipel et al., 2004). Interestingly, frontal cortex volumes do not appear to decrease with AD in DS (Beacher et al., 2009) although volumes do decline with increasing age in those without dementia (Teipel et al., 2004). Further positron emission tomography imaging using amyloid beta (Aβ)-ligands such as Pittsburgh Compound B (PiB) (Landt et al., 2011) or 2-(1-{6-[(2-[fluorine-18] fluoroethyl)(methyl)amino]-2-naphthyl}-ethylidene)malononitrile (FDDNP) (Nelson et al., 2011) show increased frontal binding after the age of 36 years (Landt et al., 2011).

Thus, the goal of the study was to specifically test the hypothesis that frontal dysfunction (measured by white matter integrity) would distinguish DS from non-DS and DS without dementia from those with dementia. Therefore, we measured WM integrity using FA with the prediction that frontal WM tracts would be particularly vulnerable to the presence of dementia in adults with DS and may also be compromised in DS relative to non-DS controls. We predicted that frontal white matter integrity would be associated with dementia in adults with DS. Therefore, we compared persons with DS and DS with clinically diagnosed dementia. These data provide an initial assessment of white matter integrity and form the basis of our efforts to evaluate longitudinal change in FA as an indicator of dementia evolution in DS.

2. Methods

2.1. Participants

Participants in this study were community residing men and women with DS, older than 35 years, recruited through local DS support groups and residential facilities in Kentucky and southern Ohio, into a longitudinal study of adult DS focused on evaluating decline in executive functioning and neural integrity as predictors of the development of dementia. Age- and gender-matched non-DS control participants provided medical history to document the absence of significant neurologic, cardiovascular and psychiatric disorders. At the time that these analyses were performed, we had 34 DS participants in the study. Four were excluded as they either could not be scanned because of a fear of the magnetic resonance imaging (MRI) scanner or there was too much motion in the MRI unit. Two participants were removed because of past traumatic brain injury or stroke. One participant was physically too large to be scanned. Two subjects had medical devices, which prevented an MRI scan. Thus, of 34 participants, 25 were able to be scanned, reflecting 73.5% of our cohort. Of the remaining 25, we had 10 demented adults with DS and thus we selected 10 age- and sex-matched nondemented DS participants to match to the 10 demented DS persons. Last, we recruited age and sex matched non-DS controls (n = 10). As a result, the final study cohort included 10 non-DS controls (CTL), 10 adults with DS (DS without dementia), and 10 DSAD (DS with AD) participants.

DS volunteers with active and unstable medical conditions (e.g., cardiovascular complications) were not included in the current sample for analysis. Thyroid dysfunction is common in individuals with DS, thus these participants were included if their thyroid dysfunction was medically controlled (DS n = 3; DSAD n = 1). Dementia diagnosis was determined through an expert consensus review of each participant with DS that involved 2 neurologists and 2 neuropsychologists using NINCDS-ADRDA criteria for dementia (McKhann et al., 1984) and included all data from medical history, medical and neurologic examinations, laboratory tests, structural imaging, mental status measures, and informant report of any changes in functional status and activities of daily living (McKhann, 1984). In addition to the objective mental status measures we obtained Dementia Questionnaire for Persons with Mental Retardation ratings from informants for each participant with DS (Evenhuis, 1996). Further, premorbid levels of functioning were derived from individual case files of existing academic and psychological test records, medical records, as well as family member interviews. Based on this information participants were categorized as low, medium, and high functioning based upon their pre-dementia level of functioning (Lott et al., 2011). Duration of dementia was established through medical records and family and/or caregiver interviews (Table 1).

All participants completed informed consent or assent (guardian consent). The study and research procedures were approved by the University of Kentucky Institutional Review Board.

2.2. Neurocognitive measures

All participants with DS completed medical, cognitive assessments, and DTI measurements obtained on the same day. The Brief Praxis Test (BPT; Dalton and Fedor, 1997) and the Severe Impairment Battery (SIB; Panisset et al., 1994) were used as neuropsychological measures for the present study. Both measures have been demonstrated to show progressive decline with worsening dementia in DS (Lott et al., 2012). Participant demographics and performances on the BPT and SIB for DS and DSAD groups are shown in Table 1. Levels of premorbid functioning did not differ between the participants with DS and DSAD (Fisher exact test $p = 0.45$) as the sample reflected a 50 of 50% split of participants in the mild and moderate ranges overall and a 20 of 30% split for those persons diagnosed with dementia. The duration of dementia in DS adults with AD ranged from 0.9 to 6.0 years (median = 3.95 years). Because of the minimal range and the sample size, we did not include this in the analysis of FA.

2.3. Imaging

All images were acquired on a 3T TIM Siemens scanner at UK Magnetic Resonance Imaging and Spectroscopy Center. DTI used an axial double refocused spin echo, echo planar imaging (EPI) sequence (repetition time = 8000 ms, echo time = 96 ms, field of view = 224 mm, 52 slices, 2 mm isotropic resolution). The DTI images were acquired with 64 noncollinear encoding directions (b = 1000 s/mm^2) and 6 images without diffusion weighting (b = 0 s/mm^2, b0).

DTI data were analyzed using FSL v4.1.5 (Functional MRI of the Brain software library, FMRIB). Raw images were pre-processed to correct for motion and residual eddy current distortion using a 12-parameter affine alignment to the corresponding b0 image via