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# Frontal White Matter Integrity in Adults with Down Syndrome with and without Dementia

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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 (AD) after 40 years of age. To detect white matter (WM) changes in the brain linked to dementia, fractional anisotropy (FA) from diffusion tensor imaging (DTI) 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 (BPT) and the Severe Impairment Battery (SIB). WM integrity differences in DS compared to CTL were found predominantly in the frontal lobes. Across all DS adults, poorer BPT 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 to controls, particularly in 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.

**Keywords:** aging, Brief Praxis Test, BPT, Dementia Questionnaire for Persons with Mental Retardation, DMR, diffusion tensor imaging, fractional anisotropy, Severe Impairment Battery, SIB, trisomy 21

## 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 to 56 years (reviewed in (Head, et al., 2007, Schupf, 2002)), AD neuropathology appears in virtually all adults with trisomy 21 after 40 years of age (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 non-invasive *in vivo* method for characterizing the microstructural properties of white matter (WM) by measuring the rate and direction of diffusion of water molecules in 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 with age-related declines on memory and executive control tasks (Bucur, et al., 2008, Gold, et al., 2010). 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. Pragmatics 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 MR structural/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 PET imaging using A $\beta$  ligands such as PiB (Landt, et al., 2011) or FDDNP (Nelson, et al., 2011) show increased frontal binding after age 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, over the age of 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 neurological, 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 due to a fear of the MRI scanner or there was too much motion in the MRI unit. Two participants were removed due to past traumatic brain injury or stroke. One participant was physically too large to be scanned. Two subjects had medical devices which prevented a 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 Alzheimer's disease) 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 two neurologists and two neuropsychologists using NINCDS-ADRDA criteria for dementia (McKhann, 1984) and included all data from medical history, medical and neurological 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 (DMR) 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 (c.f (Lott, et al., 2011)). Duration of dementia was established through medical records and family/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's Exact Test  $p=0.45$ ) as the sample reflected a 50/50% split of participants in the mild and moderate ranges overall and a 20/30% 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). Due to 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 EPI sequence (TR = 8000 ms, TE = 96 ms, FOV = 224 mm, 52 slices, 2 mm isotropic resolution). The DTI images were acquired with 64 non-collinear encoding directions ( $b = 1000 \text{ s/mm}^2$ ) and six images without diffusion weighting ( $b = 0 \text{ s/mm}^2$ ,  $b_0$ ).

Diffusion tensor imaging (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  $b_0$  image via FMRIB's Linear Image Registration Tool (FLIRT: <http://www.fmrib.ox.ac.uk/fsl>). Next, FMRIB's Diffusion Toolbox (FDT v2.0) was used to fit the diffusion tensor and calculate FA eigenvalues.

Registration of FA images into MNI152 space and subsequent voxelwise analyses followed a series of procedures known as Tract-Based Spatial Statistics (TBSS v1.2 (<http://www.fmrib.ox.ac.uk/fsl/tbss/>)) as described in detail in our previous work (Gold, et al., 2010). Briefly, all subjects' FA images were aligned to a common target using a nonlinear registration approach and then affine registered and resampled to  $1\text{mm}^3$  MNI152 space. A mean FA image was used to create a common WM tract skeleton, which was then thresholded at an FA

value of 0.2 to minimize partial volume effects after warping across subjects. Each participant's aligned FA image was subsequently projected onto the FA skeleton to account for residual misalignments between participants after the initial nonlinear registration.

This resulted in a common tract skeleton for each subject's FA image, which was filled with each participant's FA values from the centers of the nearest relevant tracts. The data are therefore in the form of a sparse 4D image with the fourth dimension being subject ID, which is treated as a random factor (Smith, et al., 2006).

All voxelwise statistical analyses were performed via a permutation-based inference for nonparametric statistical thresholding using FSL's "randomize" (Nichols and Holmes, 2002). The permutation nonparametric tests used 5000 iterations and threshold-free cluster enhancement (TFCE) to avoid the use of an arbitrary threshold in the initial cluster formation. Unless otherwise note, all randomize analyses were corrected for multiple comparisons. Results are presented in a standard format on axial slices for comparison with other studies and projected onto a 3D transparent brain for more coherent visualization.

A one-way ANOVA was used to look for FA difference between the three groups (CTL, DS, DSAD) at  $p < 0.05$ . We used two approaches for each analysis, which was to include age as a covariate and to not consider age in the ANOVA. Overall, there were no differences in the statistical outcomes from these two approaches and thus we present the analysis with age as a covariate. Significant voxels from the omnibus test were then used to perform post hoc between group comparisons of FA values within the tract skeleton using two-sample  $t$ -tests. In order to correct for group permutations, all post hoc between group  $t$ -tests were thresholded at  $p < 0.01$ . The first set of post hoc voxelwise analyses compared the 10 DS subjects and 10 age- and gender-matched controls (Analysis 1). To detect differences in WM integrity as a function of

dementia in DS, the second set of post hoc voxelwise analyses compared the 10 DS and 10 age- and gender-matched DSAD individuals (Analysis 2).

To determine the association between WM integrity and cognition, a third set of analyses used voxelwise correlations of FA and the BPT and SIB scores from all DS participants (20 subjects total) to provide sufficient power (Analysis 3). No BPT or SIB scores were available for CTL participants. A mean FA value for each participant was generated from all significant regions of interest (ROIs) resulting from Analysis 3.

To observe and detect associations between FA and the BPT and SIB for DS and DSAD separately (Analysis 4), a two-tailed Spearman correlation corrected for age and gender was performed using the average FA from significant ROIs from Analysis 3. An overlay of the significant ROIs from analyses 1 and 2, the JHU DTI-based white-matter atlas (Zhang, et al., 2005), and the MNI structural atlas (Grabner, 2006) was used to localize significant voxels within the major fiber tracts and nearest brain lobe.

### **3. RESULTS**

#### **3.1.Reduced WM Integrity in Nondemented DS Adults Relative to Age- and Gender-Matched Controls**

There were no significant voxels in the post hoc analysis for increased FA ( $p < 0.01$ ) in DS compared to CTL. Figures 1 and 2 show a post hoc analysis for decreased FA ( $p < 0.01$ ) in DS compared to CTL (blue – Analysis 1). These regions include the anterior portions of the inferior fronto-occipital fasciculus (IFOF), superior longitudinal fasciculus (SLF), forceps minor (FMin), thalamic radiations (TR), frontal and temporal portions of the uncinate fasciculus (Un), inferior longitudinal fasciculus (ILF), and the cingulum (Cin). Table 2 lists the number of

significant voxels within major fiber bundles and the cortical regions most closely associated with these WM tracts. The largest numbers of significantly lower FA voxels are in the frontal lobe when comparing DS to CTL.

### **3.2. WM integrity is decreased in Demented Adults with DS compared to DS adults without Dementia**

The DS and DSAD groups post hoc analyses yielded no significant differences when corrected for multiple comparisons at the  $p < 0.01$  level. However, to explore the possibility of more subtle differences between these two groups, we repeated these analyses using an uncorrected threshold  $p < 0.001$  and a cluster threshold of  $8 \text{ mm}^3$ . There were no significant clusters for DS having lower FA than DSAD. However, there were significant clusters for DS having greater FA than DSAD. Results are presented in Figures 1 and 2 (green - Analysis 2). Reductions in FA in DSAD participants vs. DS participants were observed in: (1) symmetric regions ( $Z=-10$ ) containing the Un, FMin, and anterior Cin; (2) left frontal regions ( $Z=7$ ) containing the FMin, IFOF, SLF, Un, Cin, and ATR; (3) symmetric regions ( $Z=7$ ) containing the Fornix(cres)/Stria Terminalis and the ATR; (4) symmetric regions ( $Z=19$ ) of the splenium containing colossal fibers and the IFOF, FMaj, SLF, and Cin.

### **3.3. Reduced FA is Associated with Poorer Cognition in DS**

No significant voxels for increased FA associated with BPT scores for DS participants with and without dementia. Areas where significant correlations of decreased FA associated with decreased BPT performance are shown (Figure 1 and 2 – red – Analysis 3). Lower BPT scores correlated with lower FA ( $p < 0.01$ ) values in (1) the anterior aspects of the body and posterior aspects of the genu of the corpus callosum ( $Z=13, 19, 24$ ); (2) the frontal lobe portions of the Cin, FMin, anterior thalamic radiations (ATR), and Un ( $Z = 6-10-19$ ); (3) the splenium of the

corpus callosum ( $Z=13, 19, \text{ and } 24$ ) and; (4) the posterior aspects of the forceps major (FMaj), IFOF, SLF, and ILF ( $Z=13, 19, \text{ and } 24$ ). Table 3 lists these and other significant voxels within major fiber bundles and their nearest brain lobes. No correlations with total SIB scores were found.

To characterize the strength of the association between BPT and average FA in DS, a two-tailed Spearman correlation correcting for age and gender was used. Higher BPT scores (indicating better cognitive function) correlated with higher FA scores (suggesting higher WM integrity;  $r=0.83, n=20, p < 0.001$ ; Figure 3).

#### **4. DISCUSSION**

These DTI data are the first published investigation of aging and dementia in DS. We observed significantly lower FA in a subset of WM tracts between adults with DS compared to similar aged non-DS controls. Many of the FA decreases we detected involved frontal circuits. Further reductions in FA were seen in demented DS adults compared to DS adults without AD. Decreased FA in DS also was associated with BPT performance suggesting a functional link between frontal executive function, but not with global cognitive status (SIB).

The results of the current study suggest that 35-65 year old adults with DS have significantly lower WM integrity than similar aged non-DS controls, particularly in the frontal lobes. It is unclear if this is inherent to DS persons at all ages or if this is unique to middle aged and older DS adults. Previous imaging studies have shown reduced frontal lobe volume in DS in children and adults without dementia (e.g. (Teipel, et al., 2004)) suggesting a strong developmental contribution to the present findings in non-demented DS adults. Our results are

also consistent with prior reports of lower MRI-based frontal volume (Teipel, et al., 2004) and lower MRI-based WM volumes in DS adults compared to non-DS controls (White, et al., 2003).

The number of trending regions from the preliminary comparison of DSAD compared to non-demented DS in the current study suggests that DTI may contribute to our understanding of the mechanisms underlying dementia development in DS, although developmental reductions in frontal cortex FA may precede dementia leaving this region more vulnerable to aging and AD in DS. Reduced frontal lobe volumes are also consistent with the earliest manifestations of dementia in DS that include changes in personality and behavior, pragnosia, and socially deficient communication (e.g. (Ball, et al., 2008)). The DTI changes demonstrated in the current study might either reflect such cortical volume loss or be a precursor to such change. We can speculate that the DTI connectivity differences seen in this study may therefore be associated with the reported striking change from previous well developed social capacities in DS with the development of dementia (Nelson, et al., 1995). Data regarding this hypothesis should emerge from this project as longitudinal scans and behavioral changes are collected.

The BPT involves 20 simple tasks to assess limb praxis (arm & leg movements), upper fine motor skills (opening a jar, picking up coins with each hand), and other highly practiced movements to simple verbal commands as well as imitation. Therefore, it is assumed to measure verbal comprehension and motor coordination and has been used in AD antioxidant clinical trials as a primary outcome measure (Lott, et al., 2011, Matsuoka, et al., 2009). The impaired ability to carry out motor activities despite intact motor function is a hallmark symptom of most diagnostic criteria for dementia and as knowledge of overlearned actions is part of the BPT assessment; memory dysfunction likely also contributes to lower BPT scores to some extent.

Research on disorders of praxis has generally involved patients with stroke and several conceptual models of praxis have been proposed (for reviews see (Koski, et al., 2002, Petreska, et al., 2007)). Key elements of these proposed brain models suggest that deficits in praxis would result from the disconnection of parietal from frontal areas as well as temporal regions involved in comprehension. In reviews by Koski and colleagues as well as Petreska and colleagues, areas such as the left dorsolateral frontal, left parietal, intraparietal sulcus and the middle frontal gyrus (among other regions) have been implicated as important regions subserving praxis. In contrast, the SIB scale incorporates some praxis tasks but this only reflects 12% of the scale. Other SIB items focus on language production and comprehension (46%) as well as memory (14%) and orientation (8%). While there were no statistically significant associations between FA and the SIB, it is possible that this reflects either the sample size, range of dementia severity, or the SIB's inclusion of more cortical functions.

The significant correlations between the BPT and FA in this study, particularly in frontal circuits, support the suggestion by Lott and colleagues that this test is sensitive to functional declines due to dementia in DS (Lott, et al., 2012). A meta-analysis by Sexton and colleagues (Sexton, et al., 2011) on DTI in mild cognitive impairment and AD shows widespread reductions in FA in the brain with the most notable and robust regions being the frontal and temporal lobes, posterior cingulum, corpus callosum, SLF and Un (Sexton, et al., 2011). All of these regions except the mid temporal regions were affected in the current study of DS when the BPT scores were correlated with FA, suggesting that dementia in DS has some similarities to dementia in the general population. The BPT correlates well with WM decline in middle aged and older adults with DS, and is particularly prominent in DS adults with dementia. Correlations between BPT and WM integrity include multiple brain regions, thus are wide spread and

consistent with regional WM declines in sporadic AD in the general population. Interestingly, there was overlap in the regions of the brain that showed reduced FA in DS as compared to age-matched control and areas in the DS brain associated with BPT scores. These included portions of frontal and parietal callosal tracts. In the frontal lobes specifically there was an overlap in forceps minor, which connects some homologous anterior frontal lobe structures. In the parietal area, the main overlap was in splenium of corpus callosum, which connects some homologous parietal structures. These connections are consistent with the BPT data because coordination of signals between homologous frontal regions and homologous parietal regions would be expected to aid planning movements and spatial relations.

Losses in WM integrity could in part reflect the influence of AD-related pathology on WM itself. Accumulating evidence suggests a potential link between WM integrity and measures of AD pathology. For example, A $\beta$  deposits have been shown to be cytotoxic to oligodendrocytes in vitro (Xu, et al., 2001) and increased levels of A $\beta$  peptides have been associated with reduced levels of myelin biochemical markers at autopsy in patients with AD (Roher, et al., 2002). The aggregation of abnormally hyperphosphorylated tau may also affect WM microstructure given that tau is predominantly found in axons and is believed to bind to and stabilize microtubules, which are essential for structural integrity axonal transport (Shahani and Brandt, 2002). Myelin degeneration has also been reported in DS autopsy cases detected by electron microscopy in individuals as young as 21 years of age (Mattiace, et al., 1991). The amount of frontal WM myelin basic protein (MBP) correlated with neuropsychological test scores, including measures of frontal function (Wang, et al., 2004). In DS, abnormalities in MBP may be related to several genes that are overexpressed in DS such as *DSCAM*, which regulates myelination (Saito, et al., 2000). The enhanced vulnerability of the frontal WM in DS



to a loss of integrity with age supports the hypothesis that late myelinating pathways may be particularly vulnerable to age and AD in DS, and that this may serve as a model for similar changes seen in late-onset sporadic AD in the general population (Stricker, et al., 2009).

An additional possible contributor to reduced FA in DS and with dementia is vascular brain injury. In the current study, it is striking that there are significant white matter differences with a somewhat periventricular distribution (Fig 2) in addition to the frontal connections and a similar pattern has been reported previously in non-DS cohorts. A recent study related white matter lesions and DTI in an autopsy cohort with AD. Ex vivo imaging of autopsy brain showed an overlap between FA and white matter lesions that reflect vascular deficits (Back, et al., 2011). White matter hyperintensities, typically prominent in periventricular regions leads to reduced FA (Chao, et al., 2013). Thus it is entirely possible that some of the WM integrity losses observed in the current study are related to vascular insufficiency or injury, further longitudinal studies may help to elucidate this as a critical factor contributing to white matter integrity losses. Indeed, longitudinal studies of FA in DS adults as they transition to dementia may provide important insights into vascular contributors to white matter integrity and cognition. In turn, findings in DS, where dementia is more strongly age-associated, may provide novel insights into the role of vascular integrity early in disease progression in AD in the general population.

## **5. SUMMARY**

The current study was based upon a relatively small sample size and our results to some extent are exploratory. However, our results suggest that WM integrity decline in DS due to AD may be similar to the declines observed in the general population with sporadic AD but with an increased impact on the frontal lobe circuitry in the DS population. These results suggest that

WM degeneration may be a mechanistic basis for some of the cognitive changes observed prior to the development of overt cortical atrophy in DSAD as cognitive function is likely to depend, in part, on the microstructural properties of WM pathways connecting distributed cortical regions. Further work elucidating the temporal relationship of reduced WM integrity, cortical atrophy, and the development of dementia in adult DS is needed, and may provide insights useful for the development of biomarkers not only for the development of DSAD, but for the global health threat of AD in the general population as well.

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**7. DISCLOSURE STATEMENT.** The authors have no actual or potential conflicts of interest.

All human subjects research was approved by the University of Kentucky Institutional Review Board.

TABLE 1. Demographics of Study Participants

Participant Characteristics	All DS	DS	DSAD	CTL
Age (mean, SD) <sup>1</sup>	51.38 (6.48)	50.61 (5.53)	52.16 (7.54)	51.07 (2.14)
Gender (men/women)	6/14	3/7	3/7	3/7
BPT (mean, SD) <sup>2</sup>	63.65 (16.78)	73.40 (4.06)	53.90 (19.15)	--
SIB (mean, SD) <sup>3</sup>	74/70 (22.04)	85.40 (11.18)	64.00 (25.45)	--
SIB Praxis (mean, SD) <sup>4</sup>	15.75 (5.06)	18.30 (2.21)	13.10 (5.88)	--
DMR (mean, SD) <sup>5</sup>	19.30 (16.49)	6.70 (3.52)	31.90 (14.44)	--
Dementia Duration (years; mean, SD)	--	--	5.31 (4.90) Median=4.15	--

Note: Paired *t*-test comparisons between the DS and DSAD are not significant for age ( $p=0.61$ ). Significant differences are seen between DS groups BPT ( $p<.01$ ), SIB ( $p<.05$ ), SIB Praxis ( $p<.05$ ), and DMR ( $p<.001$ ) scores; dementia duration is based on onset of symptoms derived from clinical interviews.

Table 2. Differences in FA between DS adults and similarly aged non-DS (CTL) participants.

<b>FA – group analysis - DS versus CTL</b>				
	Frontal	Parietal	Temporal	Occipital
Forceps - minor	2119	0	0	0
IFOF - R	1557	106	546	0
IFOF - L	1718	42	410	0
Uncinate - L	1342	59	125	0
Uncinate - R	1031	15	90	0
Genu - CC	175	0	0	0
Ant_Thal_Rad_L	1519	60	15	1
Ant_Thal_Rad_R	1124	0	4	0
SLF - L	657	1176	64	0
SLF - R	245	11	0	0
Cing_Cing Gyr - R	199	266	0	74
Cing_Cing Gyr - L	0	0	0	0
Body - CC	0	7	0	0
Cing_Hipp - L	0	0	0	0
Cing_Hipp - R	0	0	0	0
CS - L	8	118	0	0
CS - R	0	0	0	0
Splenium - CC	0	160	0	0
Forceps - major	0	7	0	0
ILF - L	0	92	473	39
ILF - R	0	0	259	0

Summary of 1 mm<sup>3</sup> voxels within major white matter fiber tracks (corresponding to blue ROIs from figure 2). The number of voxels within each lobe of the brain is listed. Note: IFOF – Inferior Frontal Occipital Fasciculus, CC – Corpus Callosum, Ant\_Thal\_Rad – Anterior Thalamic Radiations, SLF – Superior Longitudinal Fasciculus, Cing\_Cing\_Gyr – Cingulum of Cingulate Gyrus, Cing\_Hipp – Cingulum of Hippocampus, CS – Corticospinal, ILF – Inferior Longitudinal Fasciculus.

Table 3. Regions of interest that show a significant correlation between the BPT and FA in all DS participants, with and without dementia.

**FA correlation - Brief Praxis Test in DS**

	Frontal	Parietal	Temporal	Occipital
Forceps - minor	379	0	0	0
IFOF - R	25	32	0	21
IFOF - R	0	133	0	82
Uncinate - L	27	0	0	0
Uncinate - R	0	0	0	0
Genu - CC	140	0	0	0
Ant_Thal_Rad_L	83	4	0	1
Ant_Thal_Rad_R	0	0	0	0
SLF - L	0	0	0	0
SLF - R	0	3	0	0
Cing_Cing_Gyr - R	111	0	0	0
Cing_Cing_Gyr - L	0	0	0	0
Body - CC	269	29	0	0
Cing_Hipp - L	0	0	0	0
Cing_Hipp - R	0	6	0	0
CS - L	0	0	0	0
CS - R	0	0	0	0
Splenium - CC	0	520	0	3
Forceps - major	0	575	0	156
ILF - L	0	18	0	16
ILF - R	0	38	0	36

Summary of 1 mm<sup>3</sup> voxels within major white matter fiber tracks (corresponding to red ROIs from figure 2). The number of voxels within each lobe of the brain is listed. IFOF – Inferior Frontal Occipital Fasciculus, CC – Corpus Callosum, Ant\_Thal\_Rad – Anterior Thalamic Radiations, SLF – Superior Longitudinal Fasciculus, Cing\_Cing\_Gyr – Cingulum of Cingulate Gyrus, Cing\_Hipp – Cingulum of Hippocampus, CS – Corticospinal, ILF – Inferior Longitudinal Fasciculus.

**Figure Legends:**

Figure 1. FA is lower in DS compared to controls without DS, and further reduced with dementia in DS (DSAD). FA decreases in DS are associated with lower BPT scores. Images show axial slices in MNI space and illustrate representative sampling of FA analyses. Z is the voxel coordinate in MNI 1 mm template space. Yellow illustrates the underlying FA skeleton common to all participants. Blue shows areas that had reduced FA when comparing nondemented adults with DS to non-DS controls ( $p < 0.01$  corrected). Green shows areas where demented adults with DS have lower FA than nondemented adults with DS ( $p < 0.001$ , uncorrected). Red shows areas where lower FA is associated with lower BPT scores.

Figure 2. A 3D transparent view illustrating regions where FA is associated with DS, dementia and BPT scores. Blue shows areas that had reduced FA when comparing nondemented adults with DS to non-DS controls ( $p < 0.01$  corrected). Green shows areas where demented adults with DS have lower FA than nondemented adults with DS ( $p < 0.001$ , uncorrected). Red shows areas where lower FA is associated with lower BPT scores in DS adults

Figure 3. A graph illustrating the association between average brain FA from all the significant voxels from Analysis 3 (red in figures 1 and 2) and individual BPT scores in DS and DS with AD. FA is strongly correlated with BPT scores in demented individuals.

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Figure 1.









