RESEARCH ARTICLE

Altered connectivity of the default mode network in cognitively stable adults with Down syndrome: "Accelerated aging" or a prelude to Alzheimer's disease?

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Abstract

Introduction: Most individuals with Down syndrome (DS) have the neuropathological changes of Alzheimer's disease (AD) by age 40 and will have developed dementia by age 60. Alterations of the intrinsic connectivity of the default mode network (DMN) are associated with AD in the neurotypical population. In this study, we sought to determine whether, and how, connectivity between the hubs of the DMN were altered in cognitively stable adults with DS who did not have evidence of either mild cognitive impairment or AD.

Methods: Resting state functional MRI scans were collected from 26 healthy adults with DS and 26 healthy age-matched non-DS controls. Nodes comprising the DMN were generated as ROI's (regions of interest) and inter-nodal correlations estimated.

Results: Analysis of intra-network connectivity of the DMN revealed anterior-posterior DMN dissociation and hyper- and hypo-connectivity, suggesting "accelerated aging" in DS.

Discussion: Disruption of the DMN may serve as a prelude for AD in DS.

1 | INTRODUCTION

By the age of 40, virtually all adults with Down syndrome (DS), the most common genetic cause of neuro-developmental delay,[1] develop Alzheimer's disease (AD)-associated neuropathology and most will be clinically diagnosed with dementia by age 60,[2,3] although not in all cases. The triplication of amyloid precursor protein on chromosome 21 is associated with increased deposition of extracellular amyloid beta (Aβ) in the brain in DS.[4] The neuropathological hallmarks of AD, including Aβ senile plaques and tau neurofibrillary tangles, begin to develop years before cognitive impairment are observed in both the neurotypical and DS populations.[5,6] Several studies have also reported subtle early neuronal and synaptic changes in individuals with mild cognitive impairment (MCI) in the general population,[7,8] suggesting that these early pathological changes could interfere with typical patterns of brain connectivity.

Functional connectivity is a functional magnetic resonance imaging (fMRI) analysis method which compares correlations in the time-series of blood-oxygen level dependent (BOLD) activity across the brain to assess the functional relationships between distinct brain areas. Analyses of regions with comparable BOLD fluctuations over time have revealed the presence of a number of different "functional networks" in the brain. The default mode network (DMN), one of the most studied and best characterized functional networks in humans, is a group of brain regions characterized by a shared pattern of increased level of activation during rest and reduced activation during attention-demanding, externally directed tasks.[9] Regions of the classically defined DMN include: the prefrontal cortex, angular gyrus, precuneus/posterior cingulate cortex, and temporal areas.[10,11] The DMN has received particular attention in studies of neurotypical AD, in which reduced intra-network connectivity has been reported,[11–13] and is hypothesized to be associated with regional Aβ deposition.

Previous functional connectivity studies in healthy young adults with DS have suggested increases in inter-network functional connectivity of the DMN to other brain networks such as the dorsal and ventral attention networks.[14,15] However, studies focusing on the distinct components of the DMN in cognitively stable adults with DS, before clinical decline caused by AD-related neuropathology, have not as of yet been conducted. The aim of this study was to better characterize the functional architecture of the DMN in cognitively normal adults with DS. We therefore examined differences in network connectivity within the DMN in a subset of cognitively stable adults with DS (ie, no diagnosis of MCI or of dementia) and compared them to healthy age-matched adults without DS.

2 | MATERIALS AND METHODS

2.1 | Participants

Participants with DS were recruited through the Alzheimer's Disease in Down Syndrome component of the Alzheimer's Biomarker Consortium-Down Syndrome (ABC-DS), established to identify biomarkers associated with AD in older adults with DS. Massachusetts General Hospital (MGH); University of California, Irvine (UCI); and Columbia University (CU)/New York State Institute for Basic Research in Developmental Disabilities served as enrolling sites. Inclusion criteria for the overall study were: (1) ≥40 years of age at baseline; (2) estimated premorbid intelligence quotient (IQ) ≥ 30; (3) trisomy 21 as confirmed by genetic testing, and (4) English speaker. Exclusion criteria included prevalent dementia, pregnancy, or presence of nonremovable ferromagnetic material on or in the body. Premorbid level of functioning was determined from previous testing or caregiver report; a majority of individuals with DS have mild to moderate cognitive disability and this was true in our sample.[16] As part of the study design, participants with DS received a comprehensive assessment that included: (1) detailed review of medical records; (2) informant interviews focused on functional and vocational abilities, neuropsychiatric status, health status, and life events that might cause substantial stress; and (3) direct one-on-one tests covering the breadth of cognitive abilities expected to be affected by AD. Finally, each participant with DS was examined by a neurologist. Assessments of DS participants were reviewed to determine the clinical status of each participant at a Consensus Review Conference,[17] which included site senior staff members and research assistants who had direct contact with the participants under consideration. Clinical status was classified in a manner generally consistent with recommendations of the American Association on Mental Retardation-International Association for the Scientific Study of Intellectual Disability (AAMR-IASSID) Working Group for the Establishment of Criteria for the Diagnosis of Dementia in Individuals with Developmental Disability.[18,19] Categorical ratings of dementia status included: (1) cognitively stable (CS), indicating an absence of AD-related decline but allowing for age-related changes; (2) MCI-DS, indicating presence of declines over and above what would be expected with healthy aging but of insufficient severity to suggest frank dementia; (3) possible dementia, indicating presence of declines that are more severe than those of MCI-DS but of recent onset; (4) probable dementia, indicating presence of declines at least as severe as possible dementia with duration longer than 1 year. The present sample included only individuals with DS given a designation of CS who had good quality structural and resting state fMRI scans. Out of a total of 49 individuals characterized as CS, only 26 scans met sufficiently strict criteria to be included in this study (see below).

In addition, 26 age- and sex-matched healthy adults without DS served as controls (HC): all HC were recruited through MGH. The work was done in accordance with the Declaration of Helsinki after informed consent was obtained. Institutional review board approval was obtained at participating institutions; informed consent from legal authorized representatives as well as participant assent was obtained in all cases.

2.2 | Experimental design

2.2.1 | MRI image acquisition

Imaging data for participants with DS were collected across all three sites using a Siemens Prisma 3-Tesla MRI equipped with a 32-channel head coil. T1 Multi-Echo MPRAGE scans were collected with the following parameters at MGH: repetition time (TR): 2530 ms; echo time (TEs): 1.69 ms, 3.55 ms, 5.41 ms, 7.27 ms; flip angle: 7.00°, voxel sizes: 1.0 mm isotropic; image dimensions: 256 × 256 × 176; field of view (FOV): 256 × 256 mm; and with the following parameters at the CU and UCI sites: repetition time (TR): 2300 ms; echo time (TE): 2.96 ms; flip angle: 9.00°, voxel sizes: 1.0 isotropic; image dimensions: 208 × 240 × 256; FOV: 240 × 256 mm. At all sites, resting state fMRI were collected with the following parameters and in the absence of external stimuli: TR: 1250 ms; TE: 30 ms; flip angle: 90°; voxel sizes: 2.4 mm isotropic; image dimensions: 108 × 108 × 57; number of frames: 408. Imaging data from the 26 HC were collected at MGH using identical sequences.

2.2.2 | Automated anatomical segmentation

Individual T1-weighted MEMPRAGE images were automatically segmented into gray and white matter, with automated cortical parcellations and subcortical segmentations performed using the FreeSurfer reconstruction (https://surfer.nmr.mgh.harvard.edu, version 6.0). All raw imaging data and reconstructions were visually assessed for artifacts and accuracy of surface-boundary before analysis.

2.2.3 | Resting state fMRI processing

All functional images also underwent an initial visual quality assurance. In addition, after the application of the MCFLIRT tool from the FMRIB Software Library (FSL), resting state scans were eliminated from analysis if more than 10% of the frames (ie, > 40 out of 408 total frames) exceeded a threshold of 0.7 mm for framewise displacement, a measure of the translation and rotation from one frame to the next[20] as differences in motion can affect functional connectivity results.[21] We chose this threshold to avoid removing any frames of data and to control for between-group differences in motion, as clinical populations are shown to move more during scans than controls.[14] Resting state data were preprocessed with the FreeSurfer-based FS-FAST

Highlights

- Default mode network connectivity is altered in cognitively stable adults with Down syndrome (DS).
- A similar pattern of DMN connectivity is found in sporadic Alzheimer's disease (AD).
- This pattern suggests "accelerated aging" in DS or prelude to AD.

RESEARCH IN CONTEXT

1. **Systematic Review**: The authors reviewed the literature using traditional (eg, PubMed) sources and meeting abstracts and presentations. Functional connectivity using functional magnetic resonance imaging has not been widely studied in adults with Down syndrome (DS) but could provide important insights into early changes that may precede the development of Alzheimer's disease (AD). We focused our attention on the default mode network (DMN), one of the most important resting state networks affected in AD.

2. **Interpretation**: We found early alterations in DMN connectivity in cognitively stable adults with DS, in a pattern consistent with "accelerated aging," suggesting that network dysfunction could represent an early indicator or predictor of AD.

3. **Future Directions**: This article proposes a novel framework for the generation of new hypotheses related to the role of network connectivity analyses in identifying early subclinical decline in adults with DS.

analysis pipeline, which includes the following steps: motion correction, slice-timing correction, rigid anatomical-functional registration, masking of nonbrain tissue, intensity normalization, resampling of functional time series data to common surface space (fsaverage), and spatial smoothing using a 5 mm full width half maximum.

2.2.4 | Region of interest (ROI) analysis

To evaluate the architecture and connectivity of the DMN more closely, we separated Yeo's DMN from the seven-network segmentation into its major components, generating six seeds/ROIs per hemisphere.[22] These included: angular gyrus (AG), middle temporal gyrus (MTG), ventral lateral prefrontal (VLPFC), dorsal/medial prefrontal (DMPFC), precuneus/posterior cingulate cortex (PCC), and paraphippocampal gyrus. The ROIs were then transformed into subject-specific space and seeded in each subject.

2.2.5 | Whole brain voxel-wise analysis

Subject-level voxel-wise time series analysis was performed in each hemisphere to determine the Pearson's correlation coefficient for each pair of time-courses of default mode ROIs. The mean BOLD signal was measured for each of the seeded regions in each subject. The correlation coefficients between the measured time courses and every other voxel in the brain were computed, regressing out the following nuisance variables to account for physiological noise: (1) the principal component of the mean signal from cerebrospinal fluid from the lateral ventricles, (2) the principal component of the mean signal from the white matter, (3) motion parameters extracted as part of the motion correction in preprocessing, and (4) the principal component of the global (whole-brain) signal. These values were subsequently converted to z-values. Z-maps were then subjected to weighted random-effects analysis to measure statistical significance across participants at the group level. A clusterwise correction for multiple comparisons was also performed on the weighted random-effects analyses, and select results were displayed on the fsaverage inflated brain surface.[23] For each subject, partial correlation coefficients between the time-series of a given seed and ROI were calculated and compiled using the funcroi-sess and funcroi-table-sess commands from the FS-FAST FreeSurfer software package. To evaluate the within-network functional connectivity of the DMN, we conducted ROI analysis between each of the six DMN ROIs.

2.2.6 | Apolipoprotein E genotyping

ApolipoproteinE (APOE) genotyping was done using standard clinical methods.[24]

2.2.7 | Statistical analyses

Continuous variables are summarized using median and interquartile range and categorical variables (ie, sex) are summarized as percentages (frequency/number of non-missing responses). Group comparisons were performed using the either the Kruskal-Wallis or chi-square test for continuous and categorical variables, respectively.

Separate quantile regression models were constructed to quantify the associations between the Pearson correlation values of each DMN node pair and group. Additional models were constructed that simultaneously adjusted for age (modeled as a linear term as well as a functional term using restricted cubic splines), but these age adjustments did not improve the model fit via a rank score test. Unadjusted estimates of the median correlation value and its 95% confidence interval were computed by group along with estimates of the difference in these median values. To account for multiple comparisons, false discovery rate adjusted *P*-values were computed.[25]

Secondary analyses included quantifying the effect of sex and site onto connectivity for the entire cohort, and a subset analysis in which the effects of APOE $\varepsilon4$ (any $\varepsilon4$ vs not) and age were quantified among DS participants only. All analyses were performed using R 3.5.2[26] and the quantreg package.[27]

3 | RESULTS

3.1 | Demographics

Controls and participants with DS did not differ with respect to age (HC group median age 51.0 [interquartile range (IQR) 45.5–59]); DS group median age 47.5 (IQR 43.3–52.8, p = 0.124) or sex distribution (HC 15 F/11 M; DS 11 F/15 M, p = 0.267). Among the DS participants with an available APOE genotype, 15 had an $\varepsilon3/\varepsilon3$ (75%), 3 had an $\varepsilon3/\varepsilon4$ (15%), 1 had an $\varepsilon2/\varepsilon3$ (5%), and 1 had an $\varepsilon4/\varepsilon4$ (5%). APOE status was unavailable for six participants.

3.2 | Within-network group differences

We evaluated the within-group profiles of DMN connectivity based on the ROI analysis and found significant differences in intra-network connectivity of the DMN (Figure 1, Table 1). We found evidence of stronger coupling ("hyperconnectivity") between the (R)VLPFC-DMPFC (0.08, 95% confidence interval [CI]: 0.03–0.13; p = .004, p_{fdr} = 0.019) and the PCC-AG (0.09, 0.03–0.16; p = .007, p_{fdr} = 0.026), but significantly lower coupling ("hypoconnectivity") between the the (L) PCC-VLPFC (−0.07, [CI]:−0.11, −0.02; p = .006, p_{fdr} = 0.002) and the (R/L) PCC-DMPFC (−0.10 [CI]:−0.16,−0.05; p < .001, p_{fdr} = 0.003, and −0.12 [CI]−0.17,−0.06; p < .001, p_{fdr} = 0.002), for example, suggesting an anterior to posterior dissociation (see Table 1 for additional estimates).

Group differences were similar between the unadjusted and adjusted models. Thus, only unadjusted estimates are presented, to reduce the possibility of model overfitting. Similarly, associations between connectivity and APOE $\varepsilon4$ status and between connectivity and age among DS participants were not observed. We further confirmed this finding in the whole-brain voxel-wise analysis. As demonstrated in Figure 2, when the DMPFC was used as the seeded region, activation in the HC group follows the typical DMN pattern, with strong correlations to the AG, MTG, and PCC. However, in the DS group, there was significantly reduced to absent activation in the posterior DMN regions accompanied by more widespread frontal connectivity, especially to the VLPFC region. In contrast, when the PCC was used as the seeded region, there appeared to be reduced activation in the anterior DMN regions (ie, DMPFC and VLPFC) in the DS group. Similar patterns were found in both hemispheres.

4 | DISCUSSION

We examined functional connectivity within the DMN in cognitively stable Down syndrome participants and HC by comparing the functional activity between six nodes of the DMN in each hemisphere. We found a number of differences between the two groups that
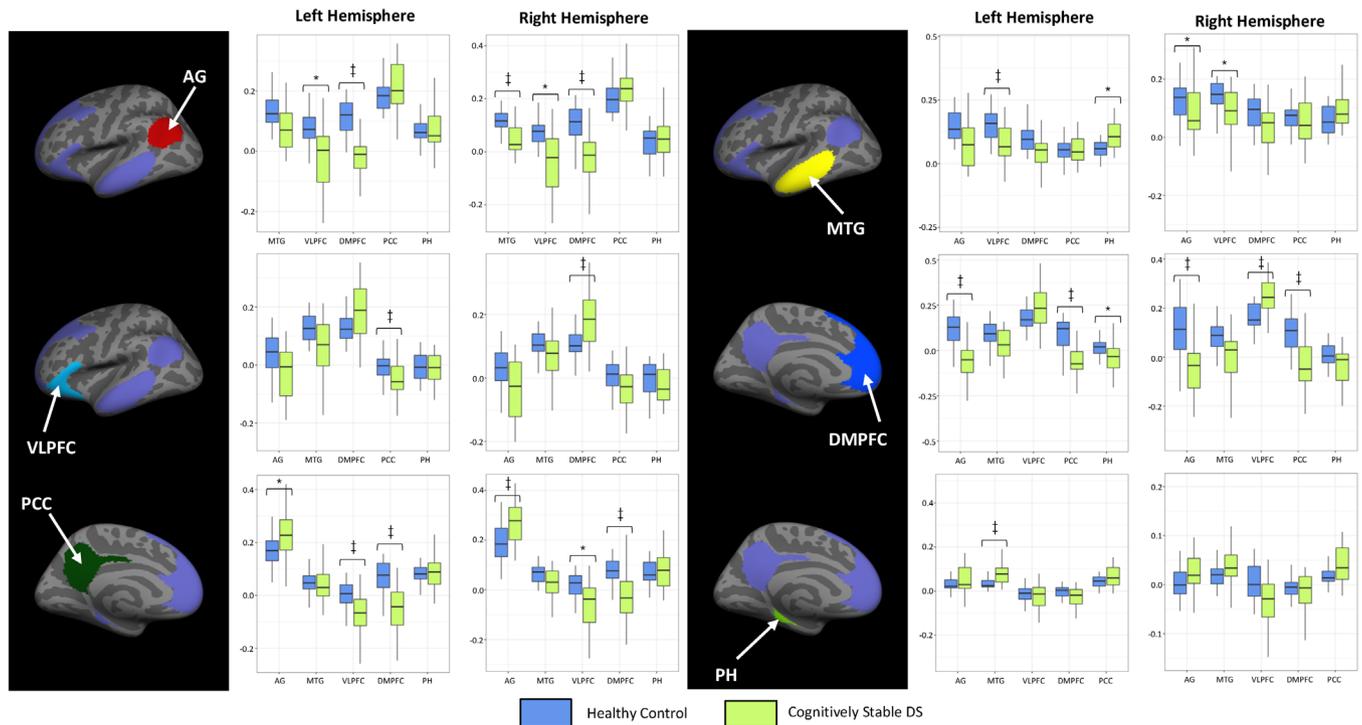
FIGURE 1 Six ROIs of the DMN selected from the Yeo seven-network parcellation for detailed connectivity analysis. Each ROI is shown on an average brain surface template, in a different color, to differentiate it from the rest of the network. Box plots depict connectivity between the given seed and the remaining five default mode network ROIs. Box plots summarize the distribution of Pearson correlation values by group with healthy controls in blue and cognitively stable DS in green. Components of the box plot include: the group median (horizontal line within each box), the 25th and 75th quantiles, and 1.5 × interquartile range (whiskers). An asterisk denotes significant unadjusted comparisons (P < .05) and a ‡ denotes significant comparisons using an FDR adjustment (P-fdr < 0.05). Abbreviations: AG, angular gyrus; DMN, default mode network; DMPFC, dorsal and medial prefrontal cortex; DS, Down syndrome; FDR, false discovery rate; MTG, middle temporal gyrus; PCC, posterior cingulate cortex/precuneus; PH, parahippocampal gyrus; ROI, region of interest; VLPFC, ventral lateral prefrontal cortex. Note that the dark blue DMPFC extends to the upper lateral surface of the frontal lobe. The ROIs are comparable on the right hemisphere and are not shown

indicate that the structure of the DMN is altered in cognitively stable adults with DS. There was a pattern of reduced functional connectivity between certain nodes of the DMN in participants with DS, in particular with those projecting to or from the frontal lobe, and a small number of connections showed stronger functional connectivity in DS subjects. The DMPFC seed showed reduced connectivity to the AG and PCC in both hemispheres. As a target ROI, the VLPFC showed reduced connectivity to MTG and PCC in the left hemisphere, as well as subthreshold reductions to these two regions in the right hemisphere and to the AG in both hemispheres. Interestingly, in the right hemisphere, the connectivity of the DMPFC and VLPMC (both frontal DMN regions) to each other was *increased*, which may indicate a higher level of local connectivity within the frontal lobe in DS.

Abnormal brain synchrony in adolescents and young adults with DS has been reported previously, demonstrating evidence of an overall simplified network structure in this population;[14] therefore, it is possible that some of our findings could reflect, at least in part, differences due to atypical brain development caused by DS, beginning in utero. Taken all together, however, our findings suggest that the anterior regions of the classical DMN (ie, those falling within the frontal lobe) are not fully integrated into the DMN in middle-aged adults with DS, perhaps because the frontal lobe in DS is more functionally connected to itself compared to the neurotypical adult brain. This hypothesis is further substantiated by examining the connections that remain "intact" in the DS population (ie, the more posterior components of the DMN). For instance, the connectivity of the AG to the PCC and PH was not significantly different in either hemisphere, nor was the connectivity of the PCC to the MTG and PH. Thus, connectivity remained relatively unchanged between regions of the DMN that fall outside of the frontal lobe, with the exception of the (R) AG-MTG and (L) PH-MTG.

The presence of an APOE ε4 allele has been associated with increases in DMN functional connectivity in young adult carriers of this allele;[28,29] however, only four participants in our DS cohort had an APOE ε4 allele, making it unlikely that this could have contributed significantly to group differences reported here. Increased activation of the DMN has been associated with amyloid deposition in the neurotypical population,[30] so it is possible that our observed increases in DMN connectivity, particularly the (R/L) VLPFC-DMPFC, could predate measurable amyloid deposition. For example, in a study using amyloid-positron emission tomography (PET) imaging, Jack et al.[31] reported increased DMN connectivity in cognitively normal neurotypical individuals who were amyloid negative at baseline but who subsequently became amyloid positive at follow-up; this pattern did not occur in those who remained amyloid negative. Amyloid accumulation begins

TABLE 1 Estimates, and 95% confidence intervals, of the median differences (Down - healthy controls) are provided by seed and target ROI and by hemisphere

		SEED					
		Angular Gyrus AG	Middle Temporal Gyrus MTG	Ventral Lateral Prefrontal VLPFC	Dorsal lateral/medial prefrontal DMPFC	Precuneus/Posterior Cingulate PCC	Parahippocampal Gyrus PH
TARGET ROI	Angular Gyrus AG	▓	-0.07* (-0.13, -0.01)	-0.05 (-0.13, 0.02)	-0.13** (-0.22, -0.05)	0.09** (0.03, 0.16)	0.02 (-0.01, 0.04)
		▓	-0.05 (-0.12, -0.01)	-0.05 (-0.12, 0.02)	-0.17** (-0.24, -0.11)	0.05* (0.00, 0.10)	0.01 (-0.03, 0.04)
	Middle Temporal Gyrus MTG	-0.09** (-0.13, -0.05)	▓	-0.02 (-0.06, 0.02)	-0.05 (-0.11, 0.00)	-0.03 (-0.07, 0.00)	0.01 (-0.01, 0.03)
		-0.05 (-0.10, -0.01)	▓	-0.04 (-0.11, 0.02)	-0.05 (-0.12, 0.01)	-0.01 (-0.05, 0.02)	0.05** (0.02, 0.07)
	Ventral Lateral Prefrontal VLPFC	-0.09* (-0.16, -0.01)	-0.05* (-0.10, 0.00)	▓	0.09** (0.04, 0.14)	-0.06* (-0.12, 0.00)	-0.03 (-0.06, 0.01)
		-0.06* (-0.13, -0.00)	-0.09** (-0.14, -0.04)	▓	0.06 (-0.01, 0.13)	-0.07** (-0.11, 0.02)	0.00 (-0.04, 0.03)
	Dorsal lateral/medial prefrontal DMPFC	-0.12** (-0.18, -0.06)	-0.04 (-0.10, 0.01)	0.08** (0.03, 0.13)	▓	-0.10** (-0.16, -0.05)	0.00 (-0.02, 0.02)
		-0.13** (-0.17, -0.08)	-0.04 (-0.08, 0.00)	0.05 (-0.01, 0.12)	▓	-0.12** (-0.17, -0.06)	-0.02 (-0.05, 0.01)
	Precuneus/Posterior Cingulate PCC	0.03 (-0.02, 0.08)	-0.02 (-0.07, 0.03)	-0.03 (-0.07, 0.01)	-0.15** (-0.21, -0.08)	▓	0.02 (-0.01, 0.04)
		0.01 (-0.04, 0.07)	0.01 (-0.03, 0.04)	-0.05** (-0.09, -0.02)	-0.18** (-0.24, -0.11)	▓	0.01 (-0.02, 0.04)
	Parahippocampal Gyrus PH	0.00 (-0.06, 0.05)	0.02 (-0.03, 0.07)	-0.04 (-0.09, 0.01)	-0.01 (-0.05, 0.04)	0.01 (-0.04, 0.06)	▓
		0.00 (-0.04, 0.04)	0.04* (0.00, 0.08)	0.00 (-0.04, 0.04)	-0.05* (-0.09, 0.00)	0.00 (-0.03, 0.04)	▓

The asterisk superscript next to the point estimate denotes significant unadjusted comparisons ($P < .05$) and the double asterisk denotes significant comparisons using an FDR-adjustment (P-fdr < 0.05).

Abbreviations: FDR, false discovery rate; ROI, region of interest.

early in DS; in one PET study, as many as 25% of nondemented adults were found to have increased uptake of Pittsburgh compound B, a tracer used to image amyloid deposition in humans in vivo.[32–34] Interestingly, the deposition of amyloid in DS follows a pattern starting first in the striatum and eventually involving rostral prefrontal-cingulo-parietal regions, to caudal frontal, rostral temporal, primary sensorimotor and occipital, and finally medio-temporal regions and the rest of the basal ganglia.[35] Therefore, the parallel between the distribution of amyloid in DS and our findings of early increased connectivity in frontal regions suggests that the observed increases in connectivity could possibly represent early changes associated with amyloid deposition.

Reduced anterior to posterior DMN node connectivity was also reported in another study in adults with DS.[36] That study, however, combined both cognitively stable and demented individuals with DS within the same analysis; our study focused on exclusively cognitively

stable adults, so a direct comparison is not possible. Reduced connectivity between nodes of the DMN has been reported in several studies of normal aging[37,38] and the present findings in our DS cohort are consistent with previous investigations reporting a dissociation between the "anterior" and "posterior" DMN connectivity within other aging populations.[25]

In our study, participants with DS demonstrated a similar pattern of reduced and/or disrupted anterior-posterior DMN connectivity; however, our participants were on average more than 20 years younger than the neurotypical population studied previously.[39] Though we did not find an association between network connectivity and age in our sample, it is tempting to speculate that the disruptions observed in cognitively stable adults with DS (which align with findings in much older neurotypical populations) reflect a sort of "accelerated" brain aging, consistent with what has been proposed previously,[40–42] including a left-ward 20-year shift in the incidence of AD in DS compared to
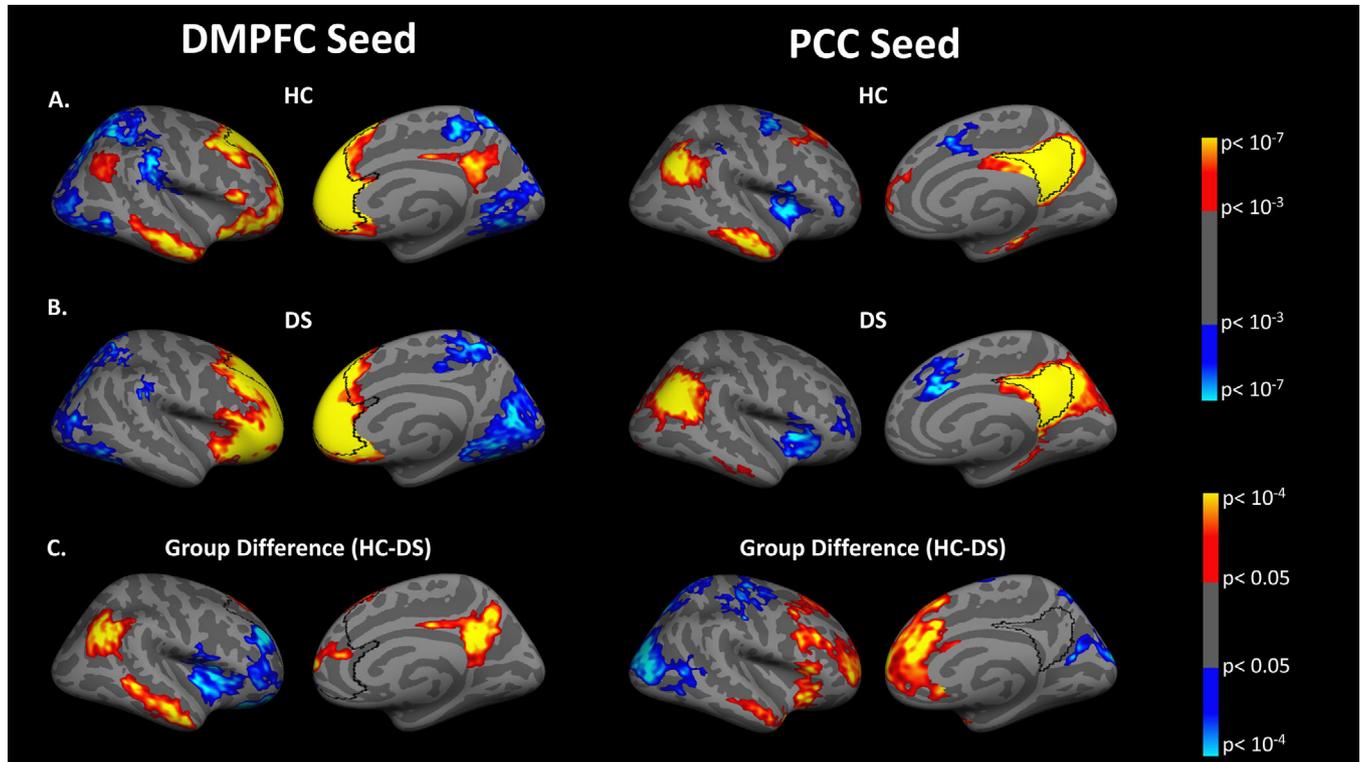
FIGURE 2 Whole brain activation surface maps for the DMPFC and PCC seed regions of the right hemisphere. HC group shown in Panel A, DS group shown in Panel B, group difference maps (HC-DS) shown in Panel C. When the DMPFC is seeded, there is reduced or no activation of the MTG, AG, or PCC in the DS group; however, when the PCC is seeded, there is reduced activation of the DMPC and VLPFC, suggesting an anterior-posterior dissociation of the DMN in DS. Maps are FDR corrected for multiple comparisons
Abbreviations: AG, angular gyrus; DMN, default mode network; DMPFC, dorsal and medial prefrontal cortex; DS, Down syndrome; FDR, false discovery rate; HC, healthy control; MTG, middle temporal gyrus; PCC, posterior cingulate cortex/precuneus; PH, parahippocampal gyrus; ROI, region of interest; VLPFC, ventral lateral prefrontal cortex.

neurotypical AD (Schupf, personal communication). Alternatively, our findings suggest that disruption of networks may be a prelude to a diagnosis of AD. However, these should only be considered hypotheses worthy of further investigation.

Several limitations of this study include its cross-sectional nature, a modest sample size, and the possibility that motion and motion artifacts, even if well controlled, could affect results. Motion is a significant challenge in imaging studies of individuals with intellectual disability and may become more so as individuals transition to dementia.

In summary, the DMN is an important resting state network with well-characterized changes in late onset Alzheimer's disease (LOAD) and normal aging. Studies including both those affected with LOAD and those diagnosed with amnestic MCI have demonstrated early functional "disconnections" or decreased functional connectivity within the DMN.[12,39,43,44] In this study, we evaluated the DMN in cognitively stable adults with DS, given the high risk for dementia caused by AD. We observed a disrupted DMN, which highlights that neuroanatomical areas are altered, even in individuals deemed to be clinically unaffected. The observed fragmentation of the DMN seems indicative of atypical brain aging and may be characteristic of functional activity

changes that occur during the preclinical stage of AD. These findings also suggest that functional connectivity MRI could serve as an important and early indicator of network disruptions in DS, before the onset of clinical diagnosis of MCI or dementia.

CONFLICTS OF INTEREST

The authors report no conflicts of interest.

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