Relatively Reduced Default Mode Network Connectivity in Comparison to The Severity of White Matter Involvement is Associated With Severe Memory Deficits and Poor Cognitive Outcomes in Patients With Idiopathic Normal Pressure Hydrocephalus.

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Research

Abstract

Background: The aim of this study was to investigate whether default mode network (DMN) connectivity and brain white matter integrity at baseline were associated with severe cognitive impairments at baseline and poor cognitive outcomes after shunt placement in patients with idiopathic normal pressure hydrocephalus (iNPH).

Methods: Twenty consecutive patients with iNPH whose symptoms were followed for 6 months after shunt placement and 10 healthy controls (HCs) were enrolled. DMN connectivity and brain white matter integrity in patients with iNPH at baseline were detected by performing resting-state functional magnetic resonance imaging with independent component analysis and by using diffusion weighted imaging with tract-based spatial statistics, respectively. Performance on the neuropsychological tests for memory and executive functions and gait test was assessed in patients with iNPH at baseline and 6 months after shunt placement.

Results: The mean DMN connectivity in the iNPH group was significantly reduced compared with that in the HC group and was significantly positively correlated with the scores of the Rey auditory verbal learning test (RAVLT) immediate recall and the frontal assessment battery (FAB). The mean fractional anisotropy of the whole-brain white matter skeleton in the iNPH group was significantly lower than that in the HC group. We divided the patients with iNPH into relatively preserved and reduced DMN connectivity groups using the indexes of DMN connectivity and white matter integrity. The reduced DMN connectivity group showed significantly worse performance on RAVLT at baseline and significantly worse improvement of RAVLT immediate recall and FAB scores compared with the preserved DMN connectivity group. Moreover, the RAVLT immediate score/the FAB score ratio highly distinguished the patients with relatively preserved DMN connectivity from those with relatively reduced DMN connectivity.

Conclusions: Our findings indicated that iNPH patients with relatively reduced DMN connectivity in comparison to the severity of brain white matter involvement are associated with severe memory deficits at baseline and poorer cognitive outcomes after shunt placement. In addition, DMN connectivity/brain white matter integrity and RAVLT immediate score/FAB score ratios are useful predictors of poor cognitive outcomes after shunt placement.

Background

Idiopathic normal pressure hydrocephalus (iNPH) is a neurological syndrome that carries no causative antecedent disease and is characterised by the clinical triad of gait disturbance, cognitive impairments, and urinary incontinence [1, 2]. The prevalence, according to the criteria of the Japanese Guidelines for iNPH [3], was between 0.51% and 2.9% [4–6]. Because iNPH is a common disease in elderly individuals and has been shown to be treatable with cerebrospinal fluid (CSF) shunt placement, an early and accurate diagnosis of iNPH has become increasingly important [1, 7]. Although the presence of disproportionately enlarged subarachnoid space hydrocephalus (DESH), especially the finding of high-

convexity tightness, on MRI or CT highly predicts shunt responsiveness [1, 8], recent studies have reported that the presence of Alzheimer's disease (AD) pathology is related to worse baseline cognitive performance and diminished postoperative outcomes in patients with iNPH [9, 10]. Brain amyloid imaging agents, such as [^{11}C]Pittsburgh compound B positron and [^{18}F]Flutemetamol emission tomography, are useful tools for detecting the presence of amyloid-β pathology in preoperative patients with iNPH [11, 12]. However, the costs of these agents are remarkably high, and these agents cannot be used for clinical examination in the Japanese health insurance system.

In our previous study, we demonstrated using diffusion tensor imaging (DTI) that brain white matter in patients with iNPH is more involved than that in patients with AD [13]. Although we compared preoperative DTI measures of brain white matter, such as fractional anisotropy (FA) and mean diffusivity (MD), between shunt-responsive and non-shunt-responsive patients with iNPH in our other study, there were no significant differences in these measures [14]. The presence of AD pathology may not strongly affect the preoperative FA and MD values in patients with iNPH. Although recent DTI studies have reported tau-related white matter alterations in patients with mild cognitive impairments (MCI) or AD, severe changes in brain white matter integrity by ventricular dilation may cloud white matter alterations due to the presence of AD pathology in patients with iNPH [15, 16]. Khoo et al. recently demonstrated that connectivity within the default mode network (DMN) measured by resting-state functional MRI is altered, and reduced DMN functional connectivity is strongly associated with executive dysfunction in patients with iNPH [17]. The DMN activates consistently during rest rather than during cognitive tasks (task negative) and is thought to be associated with monitoring the internal and external environment and memory [18–20]. In addition, hypoconnectivity within the DMN has also been observed in normal ageing and patients with MCI and AD, and it is reported to be correlated with memory deficits in patients with MCI and AD [21, 22]. The precuneus and posterior cingulate cortex are thought to play a key role in controlling the DMN, and hypometabolism or hypoperfusion in these areas is a characteristic feature of patients with AD [23, 24]. Therefore, we hypothesised that relatively reduced DMN connectivity in comparison to the severity of brain white matter involvement is related to severe cognitive decline at baseline and poor cognitive outcome after shunt placement in patients with iNPH.

The aim of this study was to investigate whether iNPH patients with severe cognitive impairments and poor cognitive outcomes after shunt placement could be detected using both indexes of DMN connectivity and brain white matter integrity at baseline. For this purpose, we used resting-state functional magnetic resonance imaging (MRI) and DTI data to measure DMN connectivity and brain white matter integrity, respectively. Furthermore, we also investigated whether preoperative clinical measures could be substitutes for the role of these MRI indexes in detecting iNPH patients with poor cognitive outcomes after shunt placement.

Methods

Participants

Twenty (8 women/12 men) consecutive patients with iNPH who underwent shunt surgery at South Miyagi Medical Center were enrolled in this study. The patients were diagnosed by board-certified neurologists based on the diagnostic criteria established according to the Japanese Clinical Guidelines for iNPH [25]. The inclusion criteria for iNPH patients in this study were as follows: (1) > 60 years of age; (2) gait disturbance, dementia, and/or urinary incontinence; (3) ventricular dilatation (Evans index > 0.3) with a narrow CSF space in the superior convexity (DESH); (4) CSF pressure < 200 mm H_2O with normal CSF cell counts and protein levels; (5) the absence of other diseases that may account for such symptoms; and (6) the lack of a previous history of illness that may cause ventricular dilatation. In addition, 10 healthy controls (HCs) who underwent medical check-ups of the brain at South Miyagi Medical Center were enrolled. The inclusion criteria for HCs were as follows: (1) > 60 years of age; (2) lack of a previous history of illness that may cause motor, cognitive, and/or urinary dysfunction; and (3) no abnormal findings on neurological examination or brain MRI. The demographic characteristics of the participants are shown in Table 1. The mean age of the iNPH group was significantly higher than that of the HC group.

Table 1
Demographic and clinical characteristics of the participants.

Variables	iNPH (n = 20)	HCs (n = 10)	P value
Age (years)	79.4 ± 6.1	70.2 ± 7.3	0.001**
Sex (women/men)	8/12	4/6	0.259
Educational attainment (years)	10.6 ± 3.1	12.1 ± 1.7	0.093
Disease duration (years)	2.4 ± 1.8		
iNPHGS			
Gait	2.0, 0−3		
Cognition	2.0, 1−3		
Urination	1.5, 0−3		
Total	5.5, 2−8		
MMSE (/30)	23.2 ± 5.0	28.1 ± 2.2	0.007*
FAB (/18)	11.9 ± 2.8	16.2 ± 1.5	< 0.001**
RAVLT			
Immediate recall (/75)	22.2 ± 9.0	39.3 ± 8.6	< 0.001**
Delayed recall (/15)	2.3 ± 2.2	8.8 ± 2.0	< 0.001**
Recognition (/30)	24.0 ± 4.4	27.9 ± 1.1	0.001**
IR/FAB ratio	1.86 ± 0.60	2.44 ± 0.55	0.017*
DR/FAB ratio	0.18 ± 0.16	0.55 ± 0.12	< 0.001**
Re/FAB ratio	2.14 ± 0.62	1.74 ± 0.18	0.058
TUG			
Time to complete (second)	17.6 ± 13.1	N/A	
Number of steps	28.9 ± 18.8	N/A	0.017*
DMN connectivity	2.751 ± 0.441	3.857 ± 1.191	0.001**
ROI FA	0.459 ± 0.021	0.481 ± 0.012	

Data are given as mean ± SD except for sex (women/men) and iNPHGS (median, range). Student's t-test was used except for sex (the chi-square test).

DMN: default mode network; DR/FAB: the delayed recall score of Rey auditory verbal learning test/the FAB score; FAB: the frontal assessment battery; HCs: healthy controls; iNPH: idiopathic normal pressure hydrocephalus; iNPHGS: the idiopathic Normal Pressure Hydrocephalus Grading Scale; IR/FAB: the immediate recall score of Rey auditory verbal learning test/the FAB score; MMSE: the Mini-Mental State Examination; N/A: not assessed; RAVLT: the Rey auditory verbal learning test; Re/FAB: the recognition score of Rey auditory verbal learning test/the FAB score; ROI FA: the mean fractional anisotropy value within the whole-brain white matter region of interest; TUG: the Timed Up and Go Test.

*$p < 0.05$. **$p < 0.005$.

All patients underwent a ventriculoperitoneal (VP) shunt procedure. Shunt implantation was conducted using a Codman-Hakim programmable valve with a Siphon-Guard (Codman and Shurtleff, Johnson and Johnson Inc.). A shunt tube was inserted in the right anterior horn of the lateral ventricle. Postoperatively, the patients were followed at the outpatient clinic, and the pressure setting of their programmable value was adjusted in a stepwise manner. Pressure adjustments were made repeatedly until the optimal pressure for each patient was attained. All patients were re-evaluated approximately 6 months after shunt surgery. Fourteen (7 female/7 male) patients showed significant shunt responsiveness, which is defined as an improvement by one or more points on the total score of the idiopathic normal pressure hydrocephalus grading scale (iNPHGS) [26].

Clinical assessments

In the present study, clinical measures were assessed prior to performing both CSF removal and shunt placement and re-assessed approximately 6 months after shunt placement. In addition to iNPHGS, we administered a gait test and a series of standard neuropsychological tests, including the Timed Up and Go test (TUG) [27], the Mini-Mental State Examination (MMSE) [28], the Frontal Assessment Battery (FAB) [29], and the Rey auditory verbal learning test (RAVLT) [30]. The FAB is a simple and well-established battery test for assessing executive/frontal lobe function. There are six subtests that assess the following aspects: (1) conceptualisation and abstract reasoning (similarities); (2) mental flexibility (phonemic verbal fluency); (3) motor programming and executive control of action (Luria motor sequences); (4) resistance to interference (conflicting instructions); (5) self-regulation and inhibitory control (go/no-go test); and (6) environmental autonomy (prehensive behaviour). Each subtest is scored from 0 to 3. The RAVLT is commonly used to assess verbal learning and memory. First, 15 words (List A) were read aloud with a one-second interval between each word for five consecutive trials. Participants were asked to repeat as many words as possible in each trial. After the fifth trial, 15 different words (List B) were read aloud, and participants were asked to repeat as many words in List B as possible. Immediately afterward, the participants were asked to recall the words in List A. After a 20-minute delay period, the subjects were asked to recall the words in List A again, and immediately after that, they were required to select the words that they had heard from a 30-word list, which included 15 previously presented words (List A) and 15 distractor words that were different from the words in List B. We used the total number of correct answers for the first five trials as the immediate recall score, the number of correct answers for a 20-

minute delayed recall trial as the delayed recall score, and the total number of true positive and true negative responses for 20-minute delayed recognition trial as the recognition score.

We used FAB and RAVLT because executive dysfunction is a characteristic feature of cognitive impairment in patients with iNPH, and memory deficits are core symptoms in patients with AD [31, 32]. Furthermore, IR/FAB, DR/FAB, and Re/FAB ratios, which are calculated by dividing the RAVLT immediate recall, delayed recall, and recognition scores by the FAB score, respectively, were defined. We assumed that these indexes represent the severity of memory deficits in comparison to the severity of executive dysfunction.

MRI procedure

Cranial MRI was performed using a GE Signal 3-Tesla MRI unit (General Electric Company, Milwaukee, WI, USA). Functional imaging and diffusion-weighted imaging (DWI) data were acquired using a single-shot spin echo-type echo planar imaging sequence. The imaging parameters used for the acquisition of the axial functional imaging data were TR 2, 500 ms, TE 30 ms, flip angle 90 degrees, 3.2 mm thickness with 0.8 mm insertion gap by 40 slices, FOV 212 × 212 mm, and matrix 64 × 64. A continuous resting-state scan was performed for approximately 6 minutes. Subjects were instructed to relax, lie still, and think about nothing as much as possible in the scanner while keeping their eyes open and remaining awake [33]. One hundred forty-four brain volumes were obtained for each subject [34]. The first four scans were discarded to avoid excluding the influence of magnetization instability. The imaging parameters used for the acquisition of the DWI data were TR 10000 ms, TE 95.2 ms, 2 mm thickness with no insertion gap by 75 slices, FOV 256 × 256 mm, and matrix 256 × 256. The axial DWI data were acquired along the 30 gradient directions, with b = 1000s/mm^2. One volume was acquired without diffusion weighting (b = 0 s/mm^2).

In addition, high-resolution structural image data were also acquired using three-dimensional spoiled gradient echo (3D-SPGR) imaging. The imaging parameters used for the acquisition of the sagittal 3D-SPGR imaging were TR 8.7 ms, TE 3.2 ms, 1.0 mm thickness with no insertion gap by 176 slices, FOV 256 × 256 mm, and matrix 256 × 256 (1-mm isotropic voxel).

Functional image data processing

Functional image data processing was performed according to the method of Khoo et al.'s study [17]. The structural images of the skull, dura, and sinuses that were obtained via 3D-SPGR imaging were stripped manually using MRIcron [35] and Wacom™ tablets (Cintiq 12WX). We used the Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC) from the FSL software package (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki) for analysing functional images. The functional images of each subject were motion corrected, and the nonbrain structures were removed. These processed images were then smoothed using a Gaussian kernel of full width at half maximum of 5 mm and temporally filtered with a high-pass filter with a cut-off frequency of 0.01 Hz. The functional images were registered to the individual's skull-stripped structural images and then normalised to the older adult–

based Montreal Neurological Institute (MNI) 152 standard space image (http://www.mccauslandcenter.sc.edu/CRNL/clinical-toolbox) using FMRIB's Nonlinear Image Registration Tool. These normalised data were used for independent component analysis (ICA) to identify large-scale patterns of functional connectivity in each group. We applied a probabilistic principal component model to estimate the optimal number of components. The normalised functional data sets were decomposed into 67 components in the iNPH group and 44 components in the HC group.

The component that most closely matched the DMN was selected using an automated 2-step process called the "goodness-of-fit" approach for each group. The standard DMN template we used to select the "best fit" was generated from the 20-dimensional ICA Brain-Map components downloaded from the FMRIB website (http://fsl.fmrib.ox.ac.uk/analysis/brainmap+rsns/). The selected component of each group is demonstrated in Fig. 1. The dual-regression approach was used to identify subject-specific time courses and spatial maps of the DMN. Consequently, the intensity of a voxel in the spatial map for each subject represented to what degree the time series of the voxel correlated with those of the DMN. To reduce between-subject variation in DMN connectivity, the intensity of each voxel was standardised using z-scale transformation in each subject. One-sample t-tests in the SPM12 software package (The Wellcome Centre for Human Neuroimaging, UCL Queen Square Institute of Neurology, London, UK) were performed to create a DMN region of interest (ROI) using the spatial maps for each group. We used a voxel-based threshold of $p < 0.001$ (uncorrected) and a cluster-based threshold of $p < 0.05$ (corrected) for significance. The mean intensity of the voxels within the DMN ROI for each group was used as a measure of DMN connectivity for each subject [17].

Diffusion-weighted image data processing

All diffusion images in each subject were aligned with the initial b0 image, and we used motion correction and registration software (eddy current correction) from the FSL software package [36]. FA maps were calculated from the diffusion weighted images for each direction using DTI calculation software from the FSL software package (DTIFIT Reconstruct diffusion tensors software). To create a whole-brain white matter ROI, we used algorithms in tract-based spatial statistics (TBSS) [37]. The initial step of TBSS consisted of determining the most representative FA map (the most typical map of the subject in the analysed groups) as the one needing the least warping for all the other maps to align to it. This map was used as the target image, and the FA maps of the subjects were nonlinearly transformed into the space of the target image for each group. The transformed FA maps were averaged to create a mean FA skeleton of the whole white matter tracts using an algorithm that found local FA maxima along the perpendicular direction of a white matter tract. An FA threshold of 0.2 was then used to differentiate between grey and white matter. We used the voxels within the mean FA skeleton in which the FA values were above 0.2 as the whole-brain white matter ROI (Fig. 2). Each subject's warped FA map was projected onto the mean FA skeleton for each group. The mean FA value within the whole-brain white matter ROI (ROI FA) was calculated as a measure of brain white matter integrity for each subject. In addition, the DMN/FA ratio, which is calculated by dividing DMN connectivity by ROI FA, was defined as the index for reflecting how reduced DMN connectivity is in comparison to the severity of brain white matter involvement.

Statistical analyses

The cognitive scores, including the scores of MMSE, FAB, RAVLT immediate recall, delayed recall, and recognition, three cognitive indexes (IR/FAB, DR/FAB, and Re/FAB ratios), DMN connectivity, and ROI FA were compared between the iNPH and HC groups using Student's t-test. In addition, because DMN connectivity and FA values of the regions in brain white matter were reported to be associated with ageing, Pearson's partial correlation coefficient corrected for age with Bonferroni correction was performed to identify potential associations between DMN connectivity and the cognitive measures (FAB score and RAVLT immediate recall, delayed recall, and recognition scores), except for the iNPHGS cognitive subscore (Spearman's partial rank correlation coefficient), and between ROI FA and these variables in the iNPH group [38, 39].

To divide the patients with iNPH into two groups, which consisted of the patients with relatively preserved DMN connectivity group and relatively reduced DMN connectivity group in comparison to the severity of brain white matter involvement, the scatterplot between DMN connectivity and ROI FA was used. A receiver operating characteristic (ROC) curve was used to identify the cut-off value of the DMN/FA ratio by which these two patient groups could be most distinguished. The differences that were observed regarding age, educational attainment, disease duration, iNPHGS total score and subscores, TUG completion time and number of steps, MMSE score, FAB score, and RAVLT immediate, delayed recall, and recognition scores between the preserved and reduced DMN connectivity groups at baseline were examined using the Mann-Whitney U-test except for sex and shunt responsiveness (Chi-square test). In addition, the Mann-Whitney U test and the Wilcoxon signed rank test were used to evaluate the variations in these clinical measures after shunt placement between the preserved and reduced DMN connectivity groups and in each patient group, respectively. Moreover, ROC curves were used to identify whether these two patient groups could be distinguished using the clinical measures that revealed significantly better performance in the preserved DMN connectivity groups. Statistical analyses were performed using IBM SPSS statistics software (version 25.00; IBM SPSS Inc., Armonk, NY, USA), and statistical significance was defined for P values < 0.05.

Results

The comparisons of the clinical and MRI measures between the iNPH and HC groups are presented in Table 1. The mean MMSE, FAB, RAVLT (immediate recall, delayed recall, and recognition), IR/FAB and DR/FAB ratios in the iNPH group were significantly lower than those in the HC group. There was no significant difference in the Re/FAB ratio between the two groups. In addition, DMN connectivity in the iNPH group was significantly reduced compared with that in the HC group, and ROI FA in the iNPH group was significantly lower than that in the HC group. The results of correlation analyses with Bonferroni correction (significance was defined for p-values < 0.05/5) are shown in Table 2. In the iNPH group, DMN connectivity was significantly positively associated with the FAB score (r = 0.613, p = 0.005) and RAVLT immediate recall score (r = 0.667, p = 0.002) and was negatively associated with the iNPHGS cognitive

subscore (r_s = -0.576, p = 0.010). There were no significant correlations between DMN connectivity and RAVLT delayed recall and recognition scores. In addition, ROI FA was not significantly correlated with FAB score, immediate recall, delayed recall, or recognition scores of RAVLT or iNPHGS cognitive subscore in the iNPH group.

Table 2
Results of correlation analyses in the iNPH group (n = 20).

Variables	DMN connectivity	ROI FA
iNPHGS cognitive	r_s = -0.576, p = 0.010*	r_s = -0.040, p = 0.872
FAB	r = 0.613, p = 0.005**	r = 0.372, p = 0.117
RAVLT immediate recall	r = 0.667, p = 0.002**	r = -0.160, p = 0.512
RAVLT delayed recall	r = 0.510, p = 0.026	r = -0.054, p = 0.826
RAVLT recognition	r = 0.552, p = 0.014	r = -0.290, p = 0.229

Pearson's partial correlation coefficient corrected for age with Bonferroni correction were used except for the iNPHGS cognitive subscore (Spearman's partial rank correlation coefficient).

DMN: the default mode network; FAB: the frontal assessment battery; iNPH: idiopathic normal pressure hydrocephalus; iNPHGS: the idiopathic Normal Pressure Hydrocephalus Grading Scale; ROI FA: the mean fractional anisotropy value within the brain white matter region of interest.

*p < 0.01. **p < 0.005.

Figure 3 demonstrates the scatterplot between DMN connectivity and ROI FA in the patients with iNPH. We divided the patients with iNPH into the preserved DMN connectivity group (n = 12) and reduced DMN connectivity group (n = 6). The remaining two patients were excluded from the following analyses. The area under the ROC curve of the DMN/FA ratio was 0.986, and the optimal cut-off value of the DMN/FA ratio was 6.285. Based on this cut-off value, the sensitivity was 91.7%, and the specificity was 100%. Figure 2-B demonstrates the plots of DMN/FA ratios in the preserved and reduced DMN connectivity groups. The comparisons of the baseline demographic and clinical and MRI measures between the preserved and reduced DMN connectivity groups are shown in Table 3. There were no significant differences in age, sex ratio, educational attainment, disease duration, total score and subscores of iNPHGS, MMSE and FAB scores, Re/FAB ratio, and completion time and number of steps of TUG, whereas the immediate recall, delayed and recognition scores of RAVLT, and IR/FAB and DR/FAB ratios in the reduced DMN connectivity group were significantly worse than those in the preserved DMN connectivity group.

Table 3
Comparison of data at baseline between the preserved and reduced DMN connectivity groups.

Variables	Preserved DMN connectivity group (n = 12)	Reduced DMN connectivity group (n = 6)	P value
Age (years)	80.5, 65−89	79.5, 73−85	0.892
Sex (women/men)	4/8	2/4	1.000
Disease duration (years)	2.5, 0.2−5.6	1.9, 0.4−5.1	0.553
Educational attainment (years)			
Responder/non-responder	10/2	3/3	0.137
iNPHGS			
Gait	2.0, 1−3	2.0, 0−3	0.750
Cognition	2.0, 1−3	2.0, 2−3	0.250
Urination	1.0, 0−3	2.0, 0−3	0.553
Total	5.0, 2−8	6.0, 2−8	0.385
MMSE (/30)	25.0, 13−29	23.0, 11−27	0.291
FAB (/18)	13.0, 9−15	12.5, 8−16	0.964
RAVLT			
Immediate recall (/75)	25.5, 14−41	18.5, 6−21	0.010*
Delayed recall (/15)	2.5, 0−9	0.5, 0−3	0.041*
Recognition (/30)	26.5, 20−30	21.5, 14−28	0.041*
IR/FAB	2.12, 1.27−2.79	1.27, 0.75−1.64	0.001**
DR/FAB	0.22, 0-0.6	0.04, 0-0.2	0.041*
Re/FAB	2.07, 1.6−2.8	0.88, 1-2.63	0.250
TUG			
Time to complete (second)	12.2, 7.2−53.7	14.7, 8.4−50.2	0.490

Variables	Preserved DMN connectivity group (n = 12)	Reduced DMN connectivity group (n = 6)	P value
Number of steps	22.0, 14−81	21.0, 16−62	0.820
DMN functional connectivity	2.961, 2.512−3.570	2.377, 1.887−3.060	0.010*
ROI FA	0.446, 0.425−0.479	0.480, 0.464−0.493	0.001**
DMN/FA	6.640, 5.860−7.454	4.953, 4.065−6.207	< 0.001**

Data are given as median and range except for sex (women/men) and shunt responsiveness (responder/non-responder). Mann-Whitney U-test was used except for sex and shunt responsiveness (the chi-square test).

DMN: default mode network; DMN/FA: DMN/FA: the default mode network connectivity/the mean fractional anisotropy value within the brain white matter region of interest; DR/FAB: the delayed recall score of Rey auditory verbal learning test/the FAB score; FAB: the frontal assessment battery; HCs: healthy controls; iNPH: idiopathic normal pressure hydrocephalus; iNPHGS: the idiopathic Normal Pressure Hydrocephalus Grading Scale; IR/FAB: the immediate recall score of Rey auditory verbal learning test/the FAB score; MMSE: the Mini-Mental State Examination; RAVLT: the Rey auditory verbal learning test; Re/FAB: the recognition score of Rey auditory verbal learning test/the FAB score; ROI FA: the mean fractional anisotropy value within the brain white matter region of interest; TUG: the Timed Up and Go Test.

*p < 0.05. **p < 0.005.

Table 4 and Supplementary Table 1 show the change in clinical measures after shunt placement in the preserved and reduced DMN connectivity groups. In the results of the Mann-Whitney U test, the FAB and RAVLT immediate recall scores in the preserved DMN connectivity group were significantly more improved than those in the reduced DMN connectivity group. On the other hand, there were no significant differences in variation in other clinical measures we examined between the two groups. The Wilcoxon signed rank test revealed significant improvements after shunt placement in all clinical measures we examined except for the iNPHGS cognition score in the preserved DMN connectivity group. In contrast, there were no significant improvements after shunt placement in any of the clinical measures we examined in the reduced DMN connectivity group.

Table 4

Variation of clinical measures after shunt placement in patients with iNPH.

Variables	Preserved DMN connectivity group (n = 12)	Reduced DMN connectivity group (n = 6)	P-value
ΔiNPHGS	-1.0, -1-0	-0.5, -1-0	0.820
Gait	0.0, -1-0	0.0, 0−0	0.437
Cognition	0.0, -1-0	0.0, -1-1	0.553
Urination	-1.0, -2-0	-0.5, -2-0	0.250
Total	2.0, 0−5	1.0, -2-9	0.213
ΔMMSE	2.0, 0−4	-1.0, -2-2	0.010*
ΔFAB	3.0, -6-8	-0.5, -2-2	0.010*
ΔRAVLT	2.0, -1-4	0.5, 0−2	0.291
Immediate recall	1.5, -1-4	-0.5, -3-4	0.180
Delayed recall	-1.4, -33.5-1.4	-2.8, -27.8-2.6	0.820
Recognition	-2.5, -49-0	-4.0, -32-2	1.000
ΔTUG			
Time to complete (second)			
Number of steps			

Δ means that a baseline value subtracted from a postoperative value. Data are given as median and range. Mann-Whitney U-test was used.

DMN: default mode network; FAB: the frontal assessment battery; HCs: healthy controls; iNPH: idiopathic normal pressure hydrocephalus; iNPHGS: the idiopathic Normal Pressure Hydrocephalus Grading Scale; MMSE: the Mini-Mental State Examination; RAVLT: the Rey auditory verbal learning test; TUG: the Timed Up and Go Test.

*$p < 0.05$.

The ROC curves of the immediate recall, delayed recall, and recognition scores of the RAVLT and IR/FAB and DR/FAB ratios for differentiating the preserved DMN connectivity group from the reduced DMN connectivity group were drawn. The areas under the ROC curves were as follows: RAVLT immediate recall score, 0.875; RAVLT delayed recall score, 0.799; RAVLT recognition score, 0.806; IR/FAB ratio, 0.944; and DR/FAB ratio, 0.799. The best predictor for distinguishing the preserved and reduced DMN connectivity

groups was the IR/FAB ratio. The ROC curve of the IR/FAB ratio yielded the optimal cut-off value of 1.652, and based on this cut-off value, the sensitivity was 83.3%, and the specificity was 100%.

Discussion

In the present study, we investigated DMN connectivity and brain white matter involvement in patients with iNPH. In addition, we examined the differences in clinical characteristics between the patients who showed relatively preserved DMN connectivity and those who showed relatively reduced DMN connectivity in comparison to the severity of brain white matter involvement. The two major findings of the study were as follows: (1) the patients with relatively reduced DMN connectivity in comparison to the severity of brain white matter involvement exhibited more severe memory impairments at baseline and poorer improvement of executive and memory functions after shunt placement than those with relatively preserved DMN connectivity; and (2) the IR/FAB ratio was the best predictor that would yield the highest sensitivity and specificity for differentiating the patients with relatively preserved DMN connectivity from those with relatively reduced DMN connectivity.

Limitation

Before discussing the implications of our findings, it is unavoidable to discuss the methodological limitations of our study. First, we did not evaluate CSF biomarkers for AD or amyloid imaging because this study was a single hospital-based study. Therefore, we could not directly prove that relatively reduced DMN connectivity in comparison to the severity of brain white matter involvement is derived from the presence of AD pathology in iNPH patients. In the future, we need to investigate the relationship among DMN connectivity, the severity of brain white mater involvement, and the presence of AD pathology. Second, the improvement of symptoms in the patients with relatively reduced DMN connectivity might be underestimated because of the small number of these patients. In particular, the iNPHGS gait subscore tended to improve after shunt placement, although this finding was not statistically significant, and 50% of these patients had shunt responsiveness defined as an improvement by one or more points on the total score of the iNPHGS. Thus, shunt placement may be effective for improving gait disturbance in patients with relatively reduced DMN connectivity. Third, the mean age of the HCs was significantly lower than that of the iNPH patients. Previous studies suggested that DMN connectivity tends to decline with ageing [40]. Therefore, we might overestimate the decrease in DMN connectivity and cognitive impairments in patients with iNPH.

DMN connectivity in patients with iNPH

In our study, DMN connectivity in the patients with iNPH was reduced compared with that in HCs. This finding was consistent with the results of Khoo et al.'s study [17]. However, DMN connectivity was positively correlated with the FAB and RAVLT immediate recall scores and was negatively correlated with the iNPHGS cognitive subscore in our study, which means that preserved DMN connectivity was linked to better cognitive performance. Surprisingly, the trend of these findings was contradictory to the results of Khoo et al.'s study [17]. Khoo et al. postulated that DMN connectivity might decrease to compensate for

impaired cognition, attention, gait, and continence in patients in the mild iNPH stage because the DMN has been thought to be one of the "task-negative" networks [18]. They also speculated that with the decline to the severe iNPH stage, the breakdown of compensatory decrease in DMN connectivity might result in an increase in DMN connectivity relative to that in the mild iNPH stage. The differences in clinical characteristics between these two studies were that the patients in our study were older and exhibited slightly milder cognitive impairments than those in Khoo et al.'s study. One possible explanation for this discrepancy between these studies is that compensation due to a decrease in DMN connectivity does not occur in very mild iNPH stages. However, the distributions of cognitive scores in our patients almost overlapped with those in Khoo et al.'s study. Moreover, there was no report that global DMN connectivity increased with increasing age in elderly individuals [40, 41]. Another possible reason is poor test-retest reproducibility for measuring DMN connectivity in patients with iNPH. The Group-ICA approach for identifying DMN connectivity has been reported to be reliable and valid [41, 42]. However, a recent study indicated that test-retest variability of resting-state networks increases with ageing and cognitive decline, and motion during MRI scanning is a confounding factor for increasing variability [43]. Thus, cognitive impairments, ageing, and/or motion during MRI scanning in patients with iNPH might cause poor test-retest reproducibility. Further large-scale cohort studies are needed to elucidate the causes of the discrepancy in the results.

iNPH patients with relatively reduced DMN connectivity

In the reduced DMN connectivity group, the RAVLT immediate recall, delayed recall, and recognition scores were significantly worse than those in the preserved DMN connectivity group. On the other hand, there was no significant difference in the FAB scores between the two groups. These findings revealed severe memory disturbances in the reduced DMN connectivity group and were consistent with our hypothesis. The proportion of iNPH patients with relatively reduced DMN connectivity in comparison to the severity of brain white matter was 40% in the present study. Several previous studies with cortical biopsy in patients with iNPH reported that AD pathology was present in 25-67.6% of patients with iNPH [9, 44, 45]. Although a small number of patients with iNPH were included in our study, the proportion of iNPH patients with relatively reduced DMC connectivity overlapped with that with the presence of AD pathology. Thus, the relatively reduced DMN connectivity in comparison to brain white matter involvement in patients with iNPH seems to be associated with the presence of AD pathology even though we did not evaluate CSF biomarkers for AD or amyloid imaging. Moreover, the reduced DMN connectivity group showed poorer improvements in RAVLT immediate recall and FAB scores after shunt placement than the preserved DMN connectivity group. Hamilton et al. reported that patients with iNPH with moderate-to-severe tau and Aβ pathology showed diminished postoperative cognitive and motor improvement compared to patients lacking AD pathology [9]. The poor cognitive outcome after shunt placement in the patients with relatively reduced DMN connectivity in our study also indicated the association between relatively reduced DMN connectivity and the presence of AD pathology.

Utility of neuropsychological tests for predicting cognitive outcomes

In the clinical measures we examined, the IR/FAB ratio was the best predictor of differentiating iNPH patients with relatively preserved DMN connectivity from those with relatively reduced DMN connectivity in comparison to the severity of brain white matter. The RAVLT immediate recall score was most strongly correlated with DMN connectivity in the patients with iNPH. In addition, the difference in RAVLT immediate recall scores between the iNPH patients with relatively preserved DMN connectivity and those with relatively reduced DMN connectivity was most statistically significant in the clinical measures we examined. Moreover, the FAB score was the most strongly associated with ROI FA, although this finding was not statistically significant. Consequently, the distribution of the IR/FAB ratio was almost consistent with that of the DMN/FA ratio in the patients with iNPH. The utility of the IR/FAB ratio for differentiating patients with relatively preserved DMN connectivity from those with relatively reduced DMN connectivity implies that iNPH patients with relatively severe memory deficits in comparison to the severity of executive dysfunction will have poor cognitive outcomes after shunt placement.

Several previous studies in iNPH reported that patients with memory deficits at baseline were less likely to show cognitive improvement, and memory deficits at baseline were the most significant predictor of dementia after shunt placement [46, 47]. Thomas et al. also reported that poor verbal immediate memory was strongly associated with poor cognitive outcomes after shunt placement [46]. This finding is coincident with our results. Memory recall is affected by attention. In particular, attention is thought to affect the success of encoding during the learning phase [48]. It was suggested that the RAVLT immediate recall score seems to reflect not only memory function but also attention. Attention decline related to executive dysfunction is one of the cognitive characteristics in patients with iNPH [31, 32]. Therefore, we speculated that the combined deficits of memory and attention due to the presence of AD pathology in patients with iNPH might make learning difficult, which leads to poor performance in RAVLT immediate recall.

Conclusions

Our study demonstrated that for iNPH patients, relatively reduced DMN connectivity in comparison to the severity of brain white matter involvement is associated with severe memory deficits at baseline and poorer cognitive outcomes after shunt placement. In addition, our results indicated that iNPH patients with relatively severe memory deficits in comparison to executive dysfunction at baseline will have poor cognitive outcomes after shunt placement. Thus, the combined indexes of DMN connectivity and brain white matter integrity and of RAVLT immediate recall and FAB scores at baseline are useful predictors of poor cognitive outcomes after shunt placement. In the future, we will try to elucidate whether relatively reduced DMN connectivity is related to the presence of AD pathology.

Abbreviations

AD: Alzheimer's disease; CSF: cerebrospinal fluid; DESH: disproportionately enlarged subarachnoid space hydrocephalus; DMN: the default mode network; DMN/FA: the default mode network connectivity/the mean fractional anisotropy value within the brain white matter region of interest; DR/FAB: the delayed

recall score of Rey auditory verbal learning test/the FAB score; DTI: diffusion tensor imaging; DWI: diffusion-weighted image; FA: fractional anisotropy; FAB: the frontal assessment battery; HCs: healthy controls; ICA: the independent component analysis; iNPH: idiopathic normal pressure hydrocephalus; iNPHGS: the idiopathic Normal Pressure Hydrocephalus Grading Scale; IR/FAB: the immediate recall score of Rey auditory verbal learning test/the FAB score; MCI: mild cognitive impairments; MD: mean diffusivity; MELODIC: the multivariate exploratory linear optimized decomposition into independent components; MMSE: the Mini-Mental State Examination; MNI: Montreal Neurological Institute; MRI: magnetic resonance imaging; RAVLT: the Rey auditory verbal learning test; Re/FAB: the recognition score of Rey auditory verbal learning test/the FAB score; ROC: a receiver operating characteristic; ROI: region of interest; ROI FA: the mean fractional anisotropy value within the whole-brain white matter region of interest; TBSS: the tract-based spatial statistics; 3D-SPGR: three-dimensional spoiled gradient echo; TUG: the Timed Up and Go Test; VP: ventriculoperitoneal.

Declarations

Ethics approval and consent to participate

We declare that the protocol of this study was approved by the ethics committee of South Miyagi Medical Center (approval numbers: 28-7 and 29-1) and has therefore been performed in accordance with the ethical standards expressed in the 1964 Declaration of Helsinki and its later amendments. We declare that all patients gave informed consent prior to inclusion in this study.

Consent for publication

Not applicable.

Availability of data and materials

Please contact the corresponding author for data requests.

Competing Interests

None declared.

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Author's contribution

SK: Study design, data acquisition, data analysis, and manuscript writing. KO, HK: Study design and data acquisition. MT: Data acquisition. NA: Data analysis. KS, KM, RO: Data acquisition. SO, HA: Shunt operation. SS: Data acquisition. KS: Manuscript editing. All authors have read and approved the final manuscript.

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References

1. Hashimoto M, Ishikawa M, Mori E, Kuwana N. Study of INPH on neurological improvement (SINPHONI). Diagnosis of idiopathic normal pressure hydrocephalus is supported by MRI-based scheme: a prospective cohort study. Cerebrospinal Fluid Res. 2010;7:18.

2. Adams RD, Fisher CM, Hakim S, Ojemann RG, Sweet WH. Symptomatic occult hydrocephalus with "normal" cerebrospinal-fluid pressure. A treatable syndrome. N Engl J Med. 1965;273:117–26.

3. Ishikawa M, Hashimoto M, Kuwana N, Mori E, Miyake H, Wachi A, et al. Guidelines for management of idiopathic normal pressure hydrocephalus. Neurol Med Chir (Tokyo). 2008;48 Suppl:S1-23.

4. Iseki C, Kawanami T, Nagasawa H, Wada M, Koyama S, Kikuchi K, et al. Asymptomatic ventriculomegaly with features of idiopathic normal pressure hydrocephalus on MRI (AVIM) in the elderly: a prospective study in a Japanese population. J Neurol Sci. 2009;277:54–7.

5. Hiraoka K, Meguro K, Mori E. Prevalence of idiopathic normal-pressure hydrocephalus in the elderly population of a Japanese rural community. Neurol Med Chir (Tokyo). 2008;48:197–9.

6. Tanaka N, Yamaguchi S, Ishikawa H, IshiiI H, Meguro K. Prevalence of possible idiopathic normal-pressure hydrocephalus in Japan: the Osaki-Tajiri project. Neuroepidemiology. 2009;32:171–5.

7. Kazui H, Miyajima M, Mori E, Ishikawa M, SINPHONI-2 Investigators. Lumboperitoneal shunt surgery for idiopathic normal pressure hydrocephalus (SINPHONI-2): an open-label randomised trial. Lancet Neurol. 2015;14:585–94.

8. Narita W, Nishio Y, Baba T, Iizuka O, Ishihara T, Matsuda M, et al. High-convexity tightness predicts the shunt response in idiopathic normal pressure hydrocephalus. AJNR Am J Neuroradiol. 2016;37:1831-1837.

9. Hamilton R, Patel S, Lee EB, Jackson EM, Lopinto J, Arnold SE, et al. Lack of shunt response in suspected idiopathic normal pressure hydrocephalus with Alzheimer disease pathology. Ann Neurol. 2010;68:535-40.

10. Kazui H, Kanemoto H, Yoshiyama K, Kishima H, Suzuki Y, Sato S, et al. Association between high biomarker probability of Alzheimer's disease and improvement of clinical outcomes after shunt surgery in patients with idiopathic normal pressure hydrocephalus. J Neurol Sci. 2016;369:236-241.

11. Leinonen V, Rinne JO, Virtanen KA, Eskola O, Rummukainen J, Huttunen J, et al. Positron emission tomography with [^{18}F]flutemetamol and [^{11}C]PiB for in vivo detection of cerebral cortical amyloid in normal pressure hydrocephalus patients. Eur J Neurol. 2013;20:1043-52.

12. Hiraoka K, Narita W, Kikuchi H, Baba T, Kanno S, Iizuka O, et al. Amyloid deposits and response to shunt surgery in idiopathic normal-pressure hydrocephalus. J Neurol Sci. 2015;356:124-8.

13. Kanno S, Abe N, Saito M, Takagi M, Nishio Y, Hayashi A, et al. White matter involvement in idiopathic normal pressure hydrocephalus: a voxel-based diffusion tensor imaging study. J Neurol. 2011;258:1949-57.

14. Kanno S, Saito M, Kashinoura T, Nishio Y, Iizuka O, Kikuchi H, et al. A change in brain white matter after shunt surgery in idiopathic normal pressure hydrocephalus: a tract-based spatial statistics study. Fluids Barriers CNS. 2017;14:1.

15. Wen Q, Risacher SL, Xie L, Li J, Harezlak J, Farlow MR, et al. Tau-related white-matter alterations along spatially selective pathways. Neuroimage. 2020;226:117560.

16. Kim WH, Racine AM, Adluru N, Hwang SJ, Blennow K, Zetterberg H, et al. Cerebrospinal fluid biomarkers of neurofibrillary tangles and synaptic dysfunction are associated with longitudinal decline in white matter connectivity: A multi-resolution graph analysis. Neuroimage Clin. 2019;21:101586.

17. Khoo HM, Kishima H, Tani N, Oshino S, Maruo T, Hosomi K, et al. Default mode network connectivity in patients with idiopathic normal pressure hydrocephalus. J Neurosurg. 2016;124:350-8.

18. Pfefferbaum A, Chanraud S, Pitel AL, Müller-Oehring E, Shankaranarayanan A, Alsop DC, et al. Cerebral blood flow in posterior cortical nodes of the default mode network decreases with task engagement but remains higher than in most brain regions. Cereb Cortex. 2011;21(1):233-44.

19. Iacoboni M, Lieberman MD, Knowlton BJ, Molnar-Szakacs I, Moritz M, Throop CJ, et al. Watching social interactions produces dorsomedial prefrontal and medial parietal BOLD fMRI signal increases compared to a resting baseline. Neuroimage. 2004;21:1167-73.

20. Kompus K. Default mode network gates the retrieval of task-irrelevant incidental memories. Neurosci Lett. 2011;487:318-21.

21. Soman SM, Raghavan S, Rajesh PG, Mohanan N, Thomas B, Kesavadas C, et al. Does resting state functional connectivity differ between mild cognitive impairment and early Alzheimer's dementia? J Neurol Sci. 2020;418:117093.

22. Pievani M, de Haan W, Wu T, Seeley WW, Frisoni GB. Functional network disruption in the degenerative dementias. Lancet Neurol. 2011;10:829-43.

23. Fransson P, Marrelec G. The precuneus/posterior cingulate cortex plays a pivotal role in the default mode network: Evidence from a partial correlation network analysis. Neuroimage. 2008;42:1178–1184.

24. Verclytte S, Lopes R, Lenfant P, Rollin A, Semah F, Leclerc X, et al. Cerebral Hypoperfusion and Hypometabolism Detected by Arterial Spin Labeling MRI and FDG-PET in Early-Onset Alzheimer's Disease. J Neuroimaging. 2016;26:207-12.

25. Mori E, Ishikawa M, Kato T, Kazui H, Miyake H, Miyajima M, et al. Guidelines for management of idiopathic normal pressure hydrocephalus: second edition. Neurol Med Chir (Tokyo). 2012;52:775-809.

26. Kubo Y, Kazui H, Yoshida T, Kito Y, Kimura N, Tokunaga H, et al. Validation of grading scale for evaluating symptoms of idiopathic normal-pressure hydrocephalus. Dement Geriatr Cogn Disord.

2008;25:37-45.

27. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc. 1991;39:142-8.

28. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12:189-98.

29. Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: a Frontal Assessment Battery at bedside. Neurology. 2000;55:1621-6.

30. Rosenerg SJ, Ryan JJ, Prifitera A. Rey Auditory-Verbal Learning Test performance of patients with and without memory impairment. J Clin Psychol. 1984;40:785-7.

31. Saito M, Nishio Y, Kanno S, Uchiyama M, Hayashi A, Takagi M, et al. Cognitive profile of idiopathic normal pressure hydrocephalus. Dement Geriatr Cogn Dis Extra. 2011;1:202-11.

32. Kanno S, Saito M, Hayashi A, Uchiyama M, Hiraoka K, Nishio Y, et al. Counting-backward test for executive function in idiopathic normal pressure hydrocephalus. Acta Neurol Scand. 2012;126:279-86.

33. Patriat R, Molloy EK, Meier TB, Kirk GR, Nair VA, Meyerand ME, et al. The effect of resting condition on resting-state fMRI reliability and consistency: a comparison between resting with eyes open, closed, and fixated. Neuroimage. 2013 Sep;78:463-73.

34. Kajimura S, Kochiyama T, Nakai R, Abe N, Nomura M. Causal relationship between effective connectivity within the default mode network and mind-wandering regulation and facilitation. Neuroimage. 2016;133:21-30.

35. Rorden C, Karnath HO, Bonilha L. Improving lesion-symptom mapping. J Cogn Neurosci. 2007;19:1081-8.

36. Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, et al. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage. 2004;23(Suppl1):S208–19.

37. Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage. 2006;31:1487–505.

38. Damoiseaux JS, Beckmann CF, Arigita EJ, Barkhof F, Scheltens P, Stam CJ, et al. Reduced resting-state brain activity in the "default network" in normal aging. Cereb Cortex. 2008;18:1856–1864.

39. Kennedy KM, Raz N. Aging white matter and cognition: differential effects of regional variations in diffusion properties on memory, executive functions, and speed. Neuropsychologia. 2009;47:916–927.

40. Oschmann M, Gawryluk JR. A Longitudinal Study of Changes in Resting-State Functional Magnetic Resonance Imaging Functional Connectivity Networks During Healthy Aging. Brain Connect. 2020;10(7):377-384.

41. Beckmann CF, Smith SM. Probabilistic independent component analysis for functional magnetic resonance imaging. IEEE Trans Med Imaging. 2004;23:137–152.

42. Jovicich J, Minati L, Marizzoni M, Marchitelli R, Sala-Llonch R, Bartrés-Faz D, et al. Longitudinal reproducibility of default-mode network connectivity in healthy elderly participants: a multicentric resting-state fMRI study. Neuroimage. 2016;124:442–454.

43. Conwell K, von Reutern B, Richter N, Kukolja J, Fink GR, Onur OA. Test-retest variability of resting-state networks in healthy aging and prodromal Alzheimer's disease. Neuroimage Clin. 2018;19:948-962.

44. Savolainen S, Hurskainen H, Paljärvi L, Alafuzoff I, Vapalahti M. Five-year outcome of normal pressure hydrocephalus with or without a shunt: predictive value of the clinical signs, neuropsychological evaluation and infusion test. Acta Neurochirur (Wien). 2002;144:515–523.

45. Leinonen V, Koivisto AM, Alafuzoff I, Pyykkö OT, Rummukainen J, von Und Zu Fraunberg M, et al. Cortical brain biopsy in long-term prognostication of 468 patients with possible normal pressure hydrocephalus. Neurodegener Dis. 2012;10:166–169.

46. Thomas G, McGirt MJ, Woodworth G, Heidler J, Rigamonti D, Hillis AE, et al. Baseline neuropsychological profile and cognitive response to cerebrospinal fluid shunting for idiopathic normal pressure hydrocephalus. Dement Geriatr Cogn Disord. 2005;20:163-8.

47. Koivisto AM, Alafuzoff I, Savolainen S, Sutela A, Rummukainen J, Kurki M, et al. Poor cognitive outcome in shunt-responsive idiopathic normal pressure hydrocephalus. Neurosurgery. 2013;72:1-8;discussion 8.

48. Craik FI, Naveh-Benjamin M, Ishaik G, Anderson ND. Divided attention during encoding and retrieval: differential control effects? J Exp Psychol Learn Mem Cogn. 2000;26:1744-9.
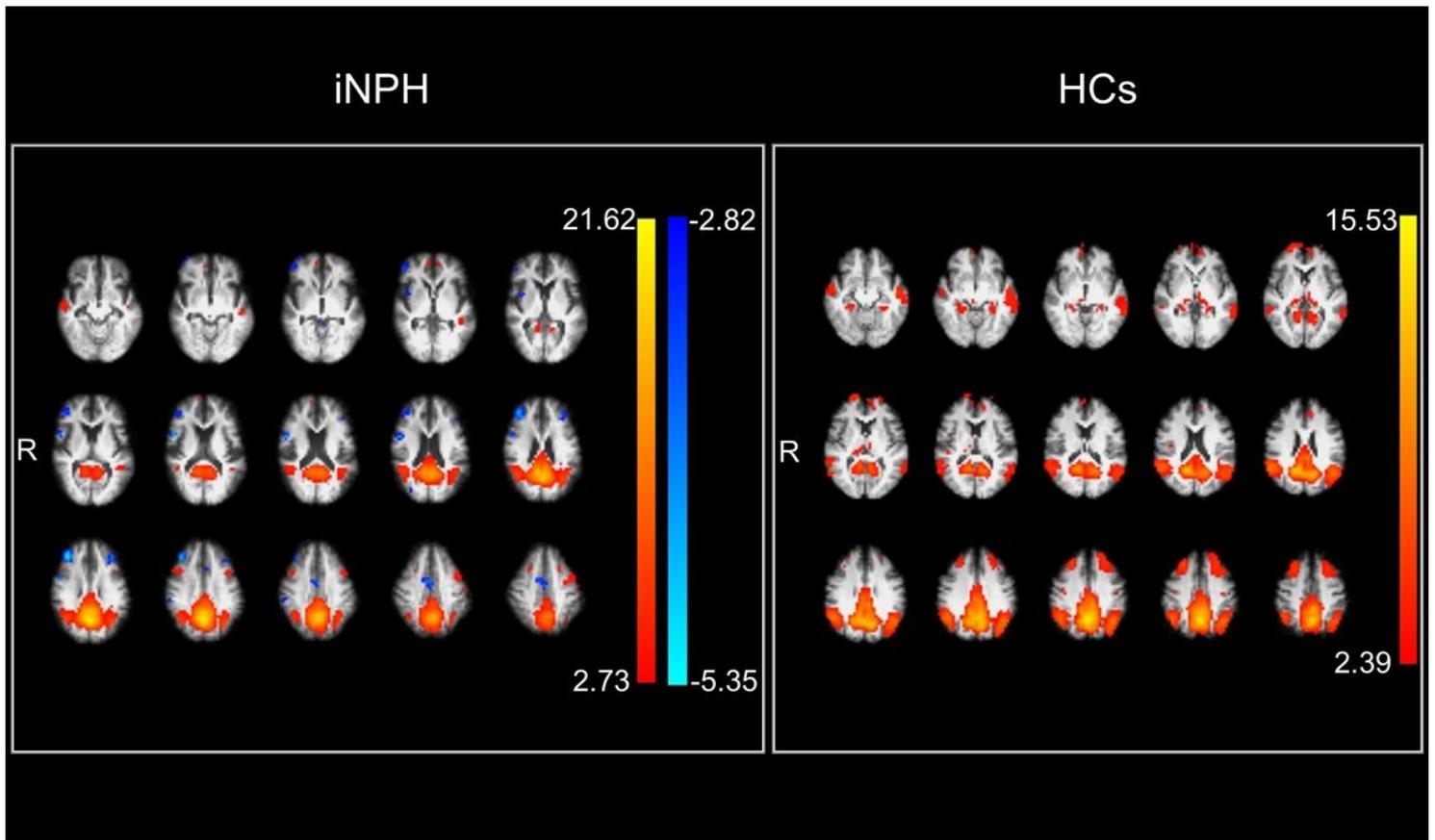
Figures

Figure 1

DMN detected by the group-ICA. Left: the patients with iNPH. Right: the HCs. The coloured bars (red-yellow and sky blue-blue) indicate z-values. iNPH: idiopathic normal pressure hydrocephalus; HCs: healthy controls; R: right.
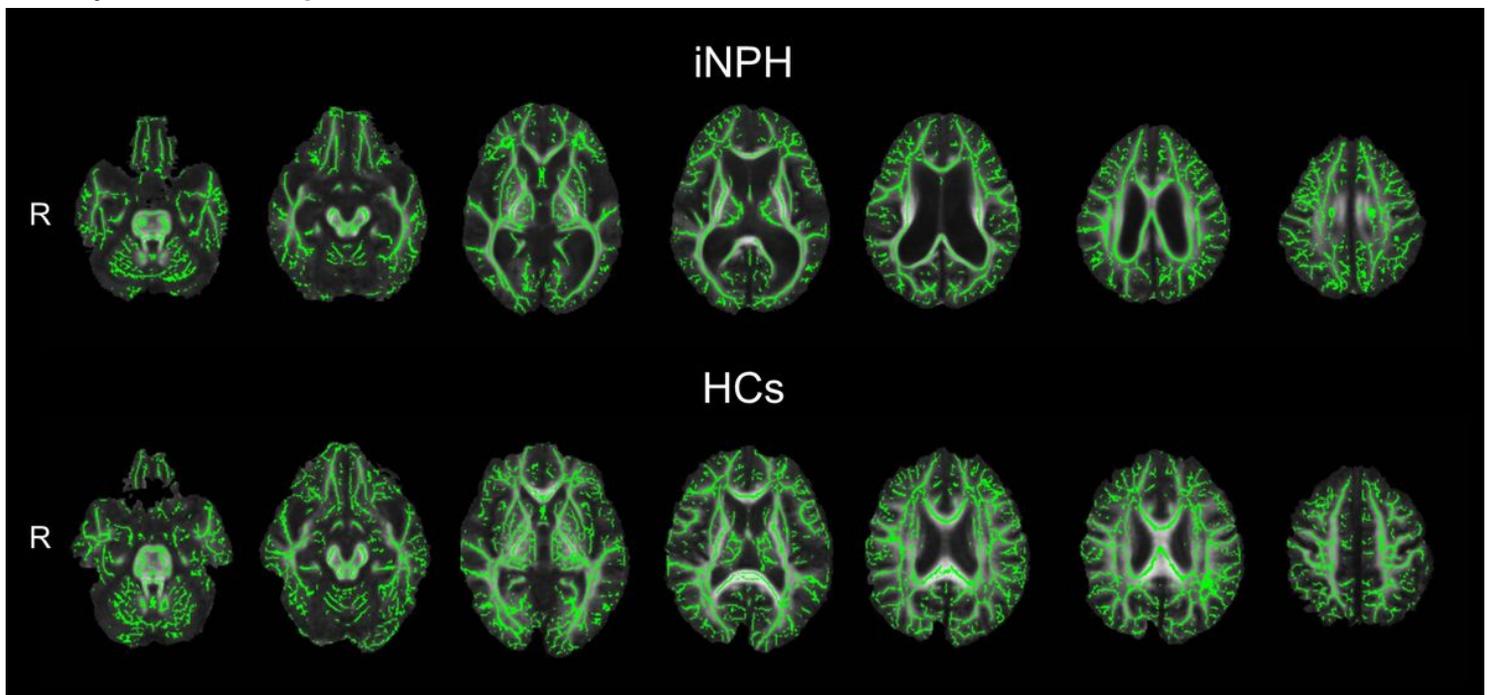

Figure 2

The mean fractional anisotropy (FA) skeletons of the whole brain white matter tracts. Upper: the patients with iNPH. Lower: the HCs. The skeleton (green) of each group is overlaid with the mean FA image of each group. iNPH: idiopathic normal pressure hydrocephalus; HCs: healthy controls; R: right.
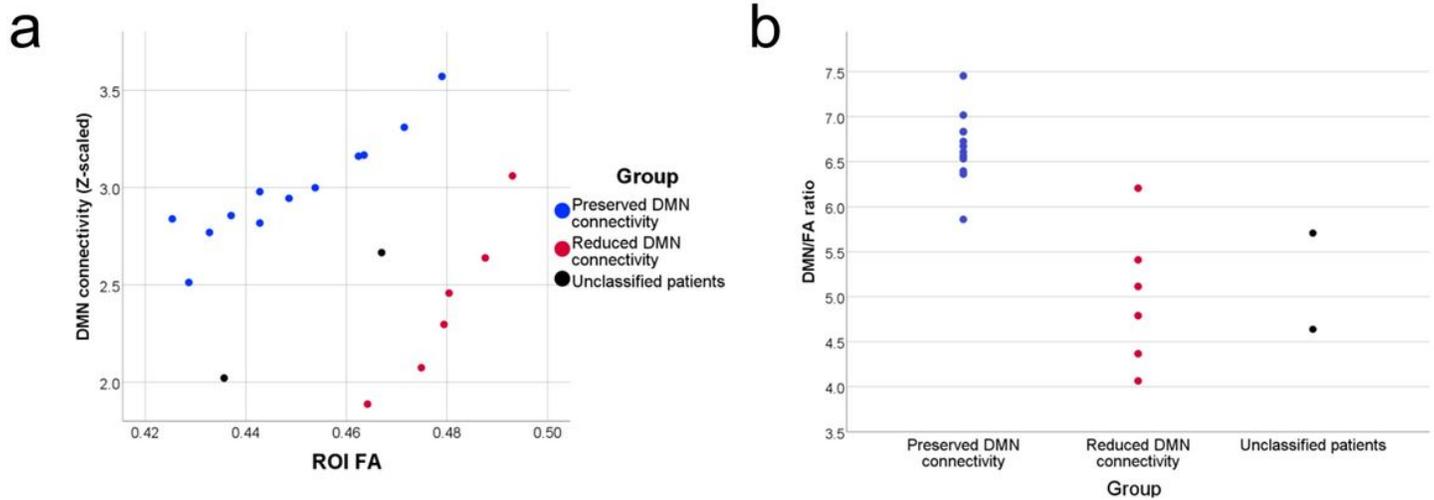

Figure 3

Association between DMN connectivity and ROI FA in patients with iNPH. a demonstrates the scatter plot between DMN connectivity and ROI FA in the patients with iNPH. Blue circles indicate the patients with relatively preserved DMN connectivity in comparison to the ROI FA (the preserved DMN connectivity group). In contrast, red circles indicate the patients with relatively reduced DMN connectivity in comparison to the ROI FA (the reduced DMN connectivity group). The remaining black circles indicate the unclassified patients. b shows the dot plots of DMN/FA ratio in the preserved and reduced DMN connectivity groups and in the unclassified patients. DMN: the default mode network; ROI FA: the mean fractional anisotropy value within the whole-brain white matter region of interest.

Supplementary Files

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- SupplementaryTable1.docx