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Similarity of functional connectivity patterns in patients with multiple sclerosis who void spontaneously versus patients with voiding dysfunction

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Abstract

Aim: To investigate if Multiple Sclerosis (MS) lesion characteristics affect functional brain connectivity (FC) during bladder voiding.

Methods: Twenty-seven ambulatory female patients with MS completed our functional magnetic resonance imaging (fMRI)/urodynamic testing (UDS) platform. Individual fMRI activation maps were generated at initiation of voiding. FC patterns of these regions were calculated and compared. Similarity of the FC pattern from one patient relative to all others was expressed by a parameter FC_{sim}. A statistical analysis was performed to reveal the relationship of the existence of an enhancing brain lesion, the size of the largest lesion and the ability to void spontaneously to this FC similarity measure.

Results: FC_{sim} values were significantly lower for patients with an enhancing MS lesion (11.7 ± 3.1 vs 5.3 ± 2.1 $P < 0.001$). Lesion size smaller than 20 mm inversely correlated significantly with FC_{sim} ($R = -0.43$, $P = 0.05$). Patients with the ability to void spontaneously had a higher FC_{sim} value (12.0 ± 2.8 vs 9.3 ± 4.4 s, $P = 0.08$). Patients that exhibited a decrease of compliance also showed a significantly lower FC_{sim} value (11.3 ± 3.5 vs 4.7 ± 0.7 , $P < 1e-5$).

Conclusion: FC connectivity analysis derived from an fMRI task-based study including repetitive voiding cycles is able to quantify the heterogeneity of connectivity patterns in the brain of MS patients. FC similarity decreased with maximum lesion size or the presence of enhancing lesions affecting the ability to void spontaneously.

Keywords

fMRI; functional connectivity; urodynamics; voiding

1 | INTRODUCTION

Any disturbance of the nervous systems that control the lower urinary tract can result in neurogenic lower urinary tract dysfunction (NLUTD).¹ NLUTD symptoms experienced by

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patients with MS can include abnormalities in the storage phase (urgency and urge urinary incontinence), voiding phase (voiding dysfunction), or both^{2,3} and may result in a variety of long-term complications such as renal insufficiency.¹

MS is a chronic multifocal demyelinating disease that can affect any part of the central nervous system (CNS). Up to 90% of patients with MS develop NLUTD within the first 18 years of the disease.^{2,4} Voiding dysfunction (hesitancy, incomplete bladder emptying, and urinary retention) requiring self-catheterization or indwelling catheters are common in MS, occurring in 34% to 79% of patients.⁵ However, urodynamic testing and urinary symptoms may not correlate in MS⁶ which illustrates the need for additional resources such as functional neuroimaging to better understand NLUTD in this complex patient population.

Demyelination of brain white matter tracts in MS may affect anatomical and functional connections of brain regions that are recruited for the executions of the voiding task. Blood oxygen dependent (BOLD) signals acquired during a functional magnetic resonance imaging (fMRI) examinations while voiding reflect brain activation/deactivation patterns revealing the neural correlates of this process.^{7,8} Functional Connectivity (FC) is the connectivity between brain regions that share functional properties. More specifically, it represents the interregional correlations between oscillations of BOLD signal time curves that are spatially remote.⁹ Task-based functional connectivity (such as voiding and evaluation of FC during urinary urgency) is suggested to be an expression of the network behavior underlying brain function and it represents a more dynamic process than BOLD signal activation. Since MS lesion locations may affect not only the regions of interest, but they may also interfere with communication between these activated regions,¹⁰ FC pattern investigations may potentially have a more meaningful implication in evaluation of NLUTD in these patients compared to BOLD patterns which just show specific regions of brain.

We hypothesize that the overall brain connectivity patterns determined with fMRI during the initiation of voiding in female patients with MS is dependent on the severity of the neurological disease, MS lesion size, and that NLUTD such as the ability to void spontaneously or loss of bladder compliance is related to this connectivity pattern.

2 | METHODS

2.1 | Subjects

The institutional review board (IRB) approved this prospective study. Twenty-seven ambulatory (with or without assistance) female patients with stable MS and NLUTD were recruited for this study. Patients were divided to two groups. Group 1; voiders ($n = 15$) and group 2; voiding dysfunction ($n = 12$) which included patients with postvoid residual of 40% of their maximum cystometric capacity or the ones who performed self-catheterization. Poor Compliance cut-off is reported vary from <10 to <30 mL/cmH₂O.^{11,12} For our study we proposed that patients whose bladder compliance was higher than 20 mL/cmH₂O were assigned to the normal compliance group, while those whose compliance was lower than 20 mL/cmH₂O were assigned to decreased compliance group. Only two patients in our cohort had decreased compliance. Prescreening prior to enrollment included an MRI safety-screening questionnaire, complete history and physical examination, a urine

pregnancy test, urinalysis, and validated questionnaires including Urogenital Distress Inventory (UDI-6), Incontinence Impact Questionnaire-7 (IIQ-7), and Hamilton Anxiety Rating Scale (HAM-A).

2.2 | fMRI examination

The detailed protocol of the fMRI examination has been reported previously.⁸ The fMRI examinations were performed at research-dedicated Food and Drug Administration (FDA)-approved full body MRI scanner located in the institutional translational research center (Philips Ingenia 3.0T, standard 12-channel head coil).

Prior to the start of the fMRI examination, double lumen 7Fr MRI-compatible bladder and rectal catheters were inserted after the subject voided spontaneously or was catheterized. Subjects were instructed to use right hand signals to indicate the times at which they reached strong desire to void, initiated voiding, and completed voiding. The bladder was gradually filled at 50 mL/min with room-temperature sterile saline until subjects signaled to indicate strong desire to urinate. After 30 s of instructed holding, subjects were given permission to initiate voiding. After voiding or attempt of voiding was completed, the cycle was repeated up to four times depending on the tolerance of the subject. High-resolution anatomical images were acquired using a 3D T1- weighted fast field echo sequence (sagittal direction, 0.7 mm in-plane resolution). Functional images were then collected concurrent with urodynamic analysis (axial echo-planar, TR = 3000 ms, 4.0 mm slice thickness, 3.38 mm in-plane resolution). Total duration of the fMRI examination was limited to 45 min.

2.3 | fMRI activation maps

fMRI image analysis was performed using the AFNI software suite (<http://afni.nimh.nih.gov/afni>). Functional and anatomical data were coregistered, and motion correction was applied to the functional data to remove drift and censor rapid movements. Significant activated voxels ($P < 0.05$) were identified at the initiation of voiding under the generalized linear model (GLM). Group level analysis was performed by transforming data into Talairach space, and significantly activated voxels were identified using a Student's *t*-test for both groups and separate averaged BOLD activation maps were created.

2.4 | FC analysis

Currently, there is no standardized approach to quantify functional brain connectivity. Common elements of a FC analysis include extracting signal time courses (BOLD effect) of brain regions (which may be anatomical areas or functional areas, such as a Brodmann regions or, as in this case, voxels in the brain) and to calculate the correlation of these signal time course (or to use a similar metric) as a connectivity measure of these brain regions. The results of this calculation is then presented in a (symmetric) matrix that contains the bivariate connectivity strengths. A variety of approaches can then be used to extract information from this adjacency matrix: for example, either connectivity strength is reported for selected brain regions or a threshold of connectivity is used to remove weak connections to report connected and unconnected regions. Both approaches in our patient populations are limited: there are too many brain regions or voxels to comprehensively use the first approach for characterizing the entire brain and variability of location of MS lesions will result in

heterogeneous connectivity maps in the second approach. We therefore introduced a similarity measure, termed FC_sim, to directly compare the adjacency matrices only of brain voxels that were activated during the voiding task (as determined by the average fMRI BOLD GLM analysis activation map), thereby omitting to further preprocess the connectivity patterns obtained from the BOLD signals of these activated voxels.

The pipeline to calculate the FC_sim parameter consisted of the following steps (please also see Figure 1):

1. BOLD signal-time courses were extracted for each voxel from the motion-corrected and spatially smoothed fMRI datasets masked with the averaged BOLD fMRI activation map mentioned above ($P < 0.05$). Individual adjacency matrices for each subject were created with Pearson correlation coefficients of the BOLD signal time courses as entries. These matrices represent the individual FC patterns.
2. To reduce dimensional complexity, the upper triangular matrix of the adjacency matrix excluding the diagonal was vectorized, thereby obtaining a unique vector corresponding to each matrix.
3. These adjacency vectors for all subjects were then concatenated by rows to form a matrix (termed “adjacency-vector matrix”). (a) A correlation matrix of the adjacency-vector matrix was calculated. Its entries represent a measure for pairwise similarity of the individual FC patterns.
4. Summing the columns of this correlation matrix results in a measure, termed the FC similarity (FC_sim) of how similar one individual FC pattern is compared to all other patterns.
5. The following graph properties characterizing the individual brain networks were calculated as average over all nodes using the R project igraph package: density, degree (average number of connections between nodes), between-ness (measure of average flow of information through nodes), modularity (number of clusters or communities that might exist in a graph), diameter (largest number of nodes which must be traversed in order to travel from one node to another) and centrality (average number of neighbors of a node).

2.5 | Statistical analysis

Data for all parameters and for the FC similarity coefficient (FCSC) were imported into R.¹³

2.5.1 | Exploratory multivariate analysis—For a first overview a multivariate analysis between all clinical parameters and all image-based parameters was performed to guide a more detailed analysis (corrplot package for the R project). A univariate correlation analysis was conducted to probe the correlation between MS lesion size and FC_sim.

2.5.2 | Student t-test analysis—Based on the results of the exploratory multivariate analysis, student t-test analyses were carried out to probe for statistical significance of differences in FC_sim in respect to the ability to void spontaneously, the presence of an

enhancing lesion and the presence of decreased bladder compliance. In addition, Student *t*-tests were carried out to probe for statistical power of the “betweenness” and “diameter” graph properties to separate patients with enhancing lesions.

Betweenness may be considered a measure of information flow in the FC graph, whereas the graph diameter is the largest number of nodes which must be traversed in order to travel from one node to another.

3 | RESULTS

3.1 | Exploratory multivariate analysis

The exploratory multivariate analysis (appendix A) with clinical parameters (provided in appendix B) revealed strong relationships (high correlation coefficient values, appendix C) between the properties of the FC graphs but not with FC_sim. The latter only showed elevated correlation with decreased bladder compliance and with the presence of an enhancing lesion parameter.

3.2 | Student *t*-test analysis

FC_sim values were statistical significantly lower for patients with an enhancing MS lesion (11.7 ± 3.1 vs 5.3 ± 2.1 $P < 0.001$). Patients that had the ability to void spontaneously had a higher FC_sim value, but the difference was not statistically significant (12.0 ± 2.8 vs 9.3 ± 4.4 s, $P = 0.08$). Patients that exhibited a decreased bladder compliance also showed a significantly lower FC_sim value (11.3 ± 3.5 vs 4.7 ± 0.7 , $P < 1e-5$).

Patients with non enhancing lesions had a higher average “betweenness” values (200 ± 31 vs 152 ± 27 , $P < 0.03$) and a larger average graph diameter (1.4 ± 0.2 vs 1.1 ± 0.06 , $P < 2e-5$). (please see Figure 2).

3.3 | Correlation analysis

The only continuous variable that showed a high correlation with FC_sim was lesion size for lesions smaller than 20 mm. A statistically inverse correlation was found ($R = -0.43$, $P = 0.05$). Two subjects with large lesions (>20 mm) were excluded as these were considered as outliers where lesion size may be confounded by other pathology.

4 | DISCUSSION

Due to the diffuse, multifocal involvement of the brain in patients with MS, urinary symptom severity and impact on quality of life may vary from patient to patient. In this study we aimed to explore functional connectivity (FC) patterns of the activated BOLD signal areas at the time of “initiation of voiding” in our cohort of MS patients in order to further elucidate similarities in the FC patterns and urinary symptoms. This evaluation may allow us to further use neuroimaging to phenotype MS patients.

The main finding of our study is the negative correlation of the similarity of functional connectivity with lesion size and the loss of similarity in the functional brain connectivity pattern with the presence of an enhancing lesions. Both larger lesion size and enhancement

of a lesion represent a more severe state of the neurological disease itself. In addition, patients with lower FC similarity expressed decreased bladder compliance (Figure 2). We attribute the high degree in the similarity of functional connectivity to a general similarity of the FC pattern in the brain of the MS patients during the performance of the above-described voiding task. The high FC similarity may be a form of compensation (ie, neuro-plasticity) the brain employs to be able to perform. It could also represent a lack of deterioration. Our analysis does not include quantifying regional analysis which limits its specificity. Compensation in MS patients has been previously reported in resting—state fMRI where increased FC in the contralateral cuneus and (ipsilateral) precuneus was found.¹⁴

These findings also support the presence of a compensation mechanism of the MS-affected brain. A longitudinal resting-state fMRI study in MS patients showed at baseline a higher levels of long-range and short-range FC with the density of these connections to be inversely correlated with disease progression.¹⁵ These results are in concordance with our findings of a loss of FC similarity in patients with advanced disease. Also, while MS patients with less severe disease were able to maintain functionality, that is, were able to void spontaneously, patients with advanced disease are not and require increased CIC or catheter drainage episodes. With the evolution of neuroimaging tools and resources, such as functional magnetic resonance imaging, we have begun to gain additional insight into brain control over bladder function in healthy individuals. Yet, our understanding of supraspinal centers and their role in initiating or modulating voiding continues to be rudimentary in patients with neurogenic (eg, Multiple Sclerosis [MS] or Stroke) or nonneurogenic voiding dysfunction (eg, underactive bladder or Fowler's syndrome). Neuroimaging studies, such as this one, that use additional analysis such as FC may augment our understanding, diagnosis, and phenotyping of patients with neurogenic bladder and voiding dysfunction.

4.1 | Limitations

MS lesions can be present in the brain and spinal cord. Appropriate lower urinary tract function relies on both the brain and spinal cord, however the initiation of voluntary voiding originates in the brain.^{7,16} In addition current neuroimaging modalities in spinal cord are limited due to challenges in imaging this structure which is smaller and mobile.¹⁷ New lesions in the spinal cord are found less often than those in the brain, the lesion volume is difficult to quantify and source of artifact in spinal cord imaging (respiratory, cardiac, and abdominal motion) are more common.¹⁸ These challenges are even more apparent when performing functional neuroimaging especially when the brain is scanned and the data regarding spine is limited to prior MRI testing. Therefore, our current study focuses only on brain lesion evaluation. For our study we selected ambulatory MS patients (with or without assistance) and a higher functional and cognitive status to decrease the potential contributions of spinal lesions on LUT.

5 | CONCLUSION

Analysis of FC_sim (brain connectivity similarity) in MS suggests that in patients with less severe disease, brain connectivity patterns are similar, whereas in those with more severe disease, connectivity patterns diverge, from both each other and the less severe cases. Those

with similar connectivity patterns also had related clinical attributes that is, spontaneous voiding.

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APPENDIX A:: CLINICAL AND IMAGING PARAMETERS

For each subject in addition to age, the following clinical parameters were recorded:

1. CIC – Clean Intermittent Catheterization
2. HAM_A: – Hamilton Anxiety questionnaire
3. UDI_6: UDI –6–Urogenital Distress Inventory 6 questionnaire
4. IIQ_7: Incontinence Impact questionnaire
5. PVR – Post Void residual
6. MCC – Maximum Cystometric Capacity/Maximum bladder capacity
7. dec_comp: Decreased compliance
8. NDO_clinic – presence of Neurogenic Detrusor Overactivity in Clinic UDS
9. DSD – presence of Detrusor Sphincter Dyssnergia in clinic UDS
10. BMI: Body Mass Index
11. deliveries: number of deliveries
12. ms_years: Duration of MS disease
13. hyst: Prior Hysterectomy
14. nocturia: Nocturia episodes
15. h_anxiety: History of anxiety
16. recent_CIC: status of Clean intermittent catheterization on most recent office visit
17. NDO_TX: Neurogenic Detrusor Overactivity treatment with oral medication
18. BTX: Intradetrusor injection of onabotulinumtoxin-A for management of urinary urgency and incontinence
19. UDI_2: Urogenital Distress Inventory 6 questionnaire, Question 2: Experience of urine leakage associated with feeling of urgency

20. UDI_5: Urogenital Distress Inventory 6 questionnaire, Question 5. Experience of difficulty for bladder voiding
21. NDO_leak: Neurogenic Detrusor Overactivity with leak in clinic UDS
22. NDO_fMRI: NDO during Fmri
23. UUI: urge urinary incontinence
24. UUI_day: urge urinary incontinence events per day
25. SUI_day: stress urinary incontinence episodes per day

Recorded parameters related to the imaging examination were as follows:

26. fMRI_dur: Duration of the fMRI task
27. enhancing: Presence of enhancing brain lesion
28. size_lesion: Size of largest lesion in mm
29. scan_time: total MRI examination scan time
30. density: network graph density
31. degree: average degree of the nodes in the network graph
32. betweenness: average betweenness of nodes in the network graph
33. diameter: diameter of network graph
34. centrality: average centrality value of nodes in network graph
35. modularity: modularity of network graph
36. FC_sim: as defined above

APPENDIX B:: VALUE OF ALL PARAMETERS

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patient #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	mean	SD	
age	40.00	52.00	44.00	38.00	56.00	58.00	37.00	57.00	66.00	57.00	47.00	42.00	36.00	53.00	39.00	45.00	85.00	45.00	69.00	56.00	35.00	45.00	33.00	48.00	48.00	71.00	65.00	50.63	12.44	
BMI	28.10	30.90	29.10	26.60	37.60	25.40	24.90	25.20	28.80	28.20	28.00	30.00	21.30	29.00	40.40	26.60	20.00	20.79	26.30	26.70	24.95	23.75	37.40	28.00	43.50	20.70	36.30	28.46	5.86	
deliveries	1.00	0.00	0.00	0.00	1.00	0.00	2.00	1.00	2.00	3.00	4.00	1.00	2.00	0.00	0.00	0.00	2.00	2.00	1.00	1.00	1.00	1.00	0.00	0.00	2.00	2.00	0.00	1.19	1.06	
h_mastectomy	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.07	0.26	
h_mastectomy_years	18.00	9.00	8.00	8.00	38.00	26.00	2.00	11.00	24.00	8.00	6.00	12.00	10.00	7.00	17.00	9.00	47.00	21.00	34.00	6.00	12.00	2.00	3.00	8.00	9.00	22.00	28.00	15.00	11.31	
spots_void	1.00	0.00	0.00	0.00	1.00	1.00	1.00	0.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.00	1.00	1.00	0.00	1.00	1.00	1.00	0.00	1.00	1.00	1.00	1.00	0.74	0.44	
CIC	0.00	1.00	1.00	1.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	0.00	1.00	0.00	0.33	0.47	
recent_CIC	0.00	1.00	1.00	1.00	0.00	0.00	0.00	1.00	0.00	1.00	1.00	0.00	0.00	0.00	0.00	1.00	1.00	0.00	1.00	1.00	1.00	1.00	1.00	0.00	0.00	1.00	0.00	0.52	0.50	
NDO_TX	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.00	0.00	1.00	0.00	1.00	0.85	0.36
BTX	1.00	1.00	1.00	1.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	1.00	1.00	0.00	1.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00	0.37	0.48	
hyst	0.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00	1.00	0.00	0.15	0.36	
UDI_6	7.00	15.00	21.00	10.00	5.00	15.00	24.00	6.00	8.00	16.00	6.00	11.00	2.00	2.00	10.00	8.00	16.00	3.00	15.00	10.00	14.00	18.00	12.00	9.00	8.00	14.00	22.00	11.37	5.82	
UDI_2	0.00	4.00	4.00	3.00	2.00	4.00	4.00	0.00	2.00	3.00	3.00	2.00	1.00	1.00	2.00	2.00	4.00	0.00	4.00	4.00	2.00	4.00	3.00	1.00	4.00	2.00	4.00	2.56	1.37	
UDI_5	3.00	4.00	4.00	4.00	1.00	4.00	4.00	3.00	2.00	4.00	0.00	2.00	0.00	0.00	2.00	2.00	4.00	3.00	3.00	4.00	4.00	2.00	4.00	4.00	0.00	4.00	4.00	2.78	1.45	
IQ_7	6.00	10.00	18.00	18.00	7.00	8.00	16.00	0.00	0.00	3.00	11.00	11.00	6.00	0.00	3.00	3.00	3.00	0.00	14.00	10.00	6.00	21.00	11.00	0.00	21.00	4.00	15.00	8.26	6.65	
HAM_A	1.00	13.00	22.00	9.00	11.00	11.00	26.00	19.00	15.00	14.00	3.00	5.00	5.00	5.00	8.00	5.00	8.00	3.00	7.00	3.00	8.00	13.00	10.00	2.00	36.00	6.00	29.00	11.00	8.57	
NDO_clinic	1.00	1.00	1.00	1.00	0.00	1.00	1.00	0.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00	1.00	1.00	1.00	0.00	1.00	1.00	0.00	0.00	1.00	0.00	1.00	0.67	0.47	
NDO_leak	0.00	1.00	1.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00	1.00	0.00	1.00	0.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	1.41	5.24	
PVR	85.00	250.00	160.00	60.00	56.00	15.00	75.00	150.00	150.00	50.00	85.00	50.00	0.00	0.00	301.00	58.00	142.00	300.00	200.00	220.00	50.00	370.00	55.00	0.00	354.00	50.00	121.70	110.22		
MCC	194.00	645.00	300.00	196.00	421.00	557.00	224.00	450.00	583.00	432.00	191.00	400.00	680.00	660.00	270.00	380.00	139.00	498.00	400.00	570.00	297.00	250.00	402.00	259.00	194.00	628.00	348.00	391.41	162.03	
PVR_max	41.81	38.76	53.33	30.61	13.30	2.69	33.48	33.33	25.73	11.57	44.50	12.50	0.00	0.00	0.00	79.21	41.73	28.51	75.00	35.69	74.07	20.00	92.04	21.24	0.00	56.37	14.37	32.64	25.58	
DSD	0.00	0.00	0.00	1.00	0.00	0.00	1.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.15	0.36	
dec_comp	0.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.07	0.26	
fMRI_dur	13.00	12.00	13.00	20.00	12.00	22.00	20.00	26.00	22.00	16.00	19.00	21.00	13.00	25.00	11.00	7.00	21.00	20.00	12.00	12.00	16.00	14.00	43.00	22.00	10.00	10.00	28.00	17.93	7.23	
NDO_MRI	0.00	1.00	1.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00	0.37	0.48		
void_MRI	1.00	1.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00	1.00	1.00	0.00	1.00	0.00	1.00	0.37	0.48		
UII	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.00	1.00	1.00	0.00	1.00	1.00	0.00	1.00	1.00	1.00	0.85	0.36	
UII_day	1.00	2.00	1.00	1.00	3.00	2.00	3.00	0.00	1.00	3.00	1.00	4.00	2.00	4.00	4.00	1.00	6.00	0.00	1.00	1.00	0.00	5.00	3.00	0.00	4.00	1.00	2.00	2.07	1.61	
SUI_day	1.00	0.00	1.00	1.00	0.00	1.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.26	0.44	
nocturia	2.00	2.00	3.00	0.00	3.00	3.00	3.00	0.00	2.00	3.00	3.00	3.00	3.00	3.00	3.00	0.00	3.00	5.00	4.00	2.00	1.00	3.00	2.00	2.00	5.00	0.00	6.00	2.41	1.55	
enhancing	0.00	1.00	1.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.15	0.36	
size_lesion	NA	10.00	12.00	NA	8.00	NA	2.00	2.00	4.00	2.00	10.00	27.00	7.00	2.00	2.00	5.00	2.00	2.00	2.00	2.00	8.00	3.00	20.00	NA	8.00	2.00	2.00	6.26	6.28	
scan_time	44.00	48.00	23.00	50.00	44.00	56.00	51.00	67.00	65.00	50.00	59.00	56.00	48.00	69.00	53.00	41.00	57.00	64.00	68.00	45.00	50.00	47.00	51.00	83.00	61.00	35.00	48.00	53.07	11.73	
voider	0.00	0.00	0.00	0.00	1.00	1.00	1.00	0.00	1.00	1.00	0.00	1.00	1.00	1.00	1.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	1.00	0.56	0.50	
density	0.41	0.65	0.66	0.60	0.35	0.44	0.58	0.36	0.46	0.45	0.54	0.42	0.32	0.45	0.48	0.48	0.34	0.24	0.40	0.41	0.41	0.42	0.31	0.45	0.34	0.35	0.47	0.44	0.10	
degree	175.72	277.94	283.15	257.15	150.94	188.12	246.81	152.41	198.97	192.34	231.71	180.29	138.75	193.22	205.45	204.77	145.11	104.88	171.92	176.74	176.69	179.59	133.58	194.27	144.03	149.15	203.60	187.31	42.74	
bevo	147.38	130.64	127.74	183.75	227.53	269.76	194.38	241.57	192.85	229.93	237.40	182.41	214.61	168.30	156.58	163.86	190.61	190.69	195.03	221.93	164.02	192.13	195.07	192.95	166.27	202.23	237.85	193.24	33.87	
diameter	1.10	1.08	1.13	1.20																										

APPENDIX C:: CORRELOGRAM OF PARAMETERS

A correlogram (diagram of correlation) of the various parameters (clinical and imaging-related) as a multivariate analysis was created to guide a more detailed investigation of the relations of different parameters with each others.

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FIGURE 1.

A, Representative FC networks in the anatomical space of the human brain. Subject 1 has low FC_sim, subject 4 high FC_sim. B, Adjacency matrices representing the FC networks shown in (A). Columns and rows represent all the voxels in the brain that exhibited on average a significant increase in BOLD effect during the initiation of voiding. Positive correlations between the BOLD signal time courses of each voxel are shown in red, negative correlations are shown in blue. Each entry represented a bivariate measure of connective strength between two voxels. Positive correlations are shown in A as connections between brain regions. C, The correlation matrix of the adjacency vector matrix discussed in the text. Magnitude of values are indicated by the size of the circles. Subjects 1–5 and 19 have predominantly low values. FC similarity (FC_sim) defined as the column sums of the correlation matrix is consequently low for these subjects (shown in a bar plot at the bottom of the figure). Positive correlations are displayed in blue and negative correlations in red color (not to be confused with the customary BOLD signal color-coding for fMRI). Color intensity and the size of the circle are proportional to the correlation coefficients

FIGURE 2.

Upper row: Left: Correlation between FC_sim and lesion size (size_lesion) Right: Box plot of difference in FC_sim for patients that showed decreased compliance. Lower row: Left: Results of Student *t*-tests differentiating MS patients with enhancing and non-enhancing lesions and, right, patients that are able to void spontaneously