Supplementary Methods

Subjects' inclusion and exclusion criteria. Healthy subjects with no previous history of neurological, psychiatric, or cardiovascular disorders and a normal neurological examination, were recruited. To be included, patients had to be in the remission phase of a first episode suggestive of demyelination, and had to have a complete neurological examination with rating of the Expanded Disability Status Scale (EDSS) score[1] and a brain MRI scan acquired within two months of the onset of symptoms. Exclusion criteria were: contraindication to MRI; acute phase of a clinical episode suggestive of demyelination or steroid administration during the month prior to study inclusion; a history of major medical, neurological, or psychiatric disorders as well as drug and alcohol abuse. Appropriate investigations were carried out as necessary to exclude alternative diagnoses, and all patients were carefully interviewed to rule out possible previous events.

None of the subjects included in this cohort was used in previous MRI studies.

MRI acquisition. Using a 1.5 T system (Achieva; Philips Medical Systems, Eindhoven, The Netherlands) under a program of regular maintenance (no major hardware or software upgrades occurred during the study), the following brain images were acquired from all subjects within 48 hours of the neurological evaluation, at the different study time-points: a) resting state (RS) functional MRI (fMRI) for static and dynamic RS functional connectivity (FC) assessment: T_2*-weighted echo-planar imaging sequence (repetition time [TR]=3000 ms; echo time [TE]=35 ms; flip angle=90°, 200 sets of 30 axial slices after automatic discard of the first two images, parallel to the anterior commissure-posterior commissure plane, with a thickness of 4 mm, an in-plane resolution=1.88×1.88 mm^2 and an acquisition matrix=96×96, reconstructed to 128×128). Total acquisition time of the RS fMRI sequence was 10 min 3 s. During RS fMRI scanning, subjects were instructed to keep their eyes closed, to remain motionless and not to think anything particular. All subjects reported that they had not fallen asleep during scanning, according to a questionnaire delivered immediately after the MRI session; b) dual-echo (DE) turbo-spin-echo: TR=3124 ms, TE=20/100 ms, echo train length=6; 44 contiguous axial slices, pixel size=0.94×0.94×3.0 mm^3, flip

angle=90º, matrix=256×256, FOV=240×240 mm^2; c) 3D T_1-weighted scan: TR=7.2 ms; TE=3.27 ms; inversion time [TI]=1000 ms; flip angle 8º; 180 axial slices with voxel size=1.0×1.0×1.0 mm, matrix=256×256, field of view (FOV)=256×256 mm^2; and d) post-contrast (0.1 mmol/kg of gadopentetate dimeglumine; acquisition delay 5 min) T_1-weighted spin echo (SE) scan: TR=500 ms; TE=10 ms; flip angle 90º; 44 contiguous axial slices, pixel size=0.94×0.94×3.0 mm^3, matrix=256×256, FOV=240×240 mm^2.

In clinically isolated syndrome (CIS) patients, sagittal short tau inversion recovery and post-contrast T_1-weighted turbo-spin-echo scans of the cervical cord were also acquired for routine clinical purposes and used for lesion count analysis.

All imaging was performed according to published guidelines.[2]

Structural MRI analysis. At baseline, T_2-hyperintense, T_1-hypointense and gadolinium-enhancing lesions were identified by consensus by two experienced observers blinded to patients' identity. On follow-up scans, the numbers of new T_2-hyperintense, T_1-hypointense and gadolinium-enhancing lesions were assessed. From the lesion classification and count (including both brain and cervical cord lesions), fulfilment of the criteria for disease dissemination in space and time was assessed.[3]

Brain T_2-hyperintense and T_1-hypointense lesion volumes were quantified using the Jim software package (Version 7, Xinapse Systems, Colchester, UK). After refilling of T_1-hypointense lesions, baseline normalized brain volumes and percentage brain volume change (PBVC) were calculated using the SIENAx and SIENA programs.

From T_2 lesions, binarized masks were obtained, co-registered to the 3D T_1-weighted scans (using the rigid transformation between the T_2-weighted and the 3D T_1-weighted image), normalized to the standard MNI space and averaged to obtain T_2 lesion probability maps. This procedure was repeated for each study time-point.

RS fMRI data pre-processing. Data were processed using a combination of toolboxes, as previously suggested.[4] We performed rigid head motion correction using SPM12 software. Then, RS fMRI data were de-spiked using the AFNI3s 3dDespike algorithm to mitigate the impact of outliers, and

co-registered to the corresponding 3D T_1-weighted scan. Using SPM12, data were subsequently warped to the Montreal Neurological Institute (MNI) template and resampled to a 2 mm^3 isotropic voxel size. Instead of Gaussian smoothing, we smoothed the data to 6 mm full width at half maximum (FWHM) using AFNI3s BlurToFWHM algorithm which performs smoothing using a conservative finite difference approximation to the diffusion equation.[5]

Group independent component analysis, selection of networks of interest and overlay with T_2 lesion distribution. Pre-processed data from healthy controls (HC) and patients were analyzed using spatial group independent component analysis (ICA) and the GIFT software,[6, 7] following three main steps: (i) data reduction, (ii) group ICA (repeated 20 times in ICASSO to ensure stability), and (iii) back reconstruction. The number of group independent components (ICs) was set to 100, to ensure comparability of dynamic FC analysis with previous studies.[8-11] Subject-specific spatial maps and time courses were back-reconstructed using the spatio-temporal regression approach.[6, 7] Visual inspection of the spatial patterns, a frequency analysis of the spectra of the estimated ICs and a template-matching procedure (using the component provided by Allen *et al.*[4] as reference templates) allowed the removal of components clearly related to motion and physiological artefacts, and the selection of 41 relevant ICs of interest (rICs).

Spatial maps of the eight functionally relevant networks included in this study (i.e., sensorimotor, visual, auditory, executive, temporal, default mode, attention and cerebellar networks) were calculated by merging the rICs masks assigned to each network. Then, the percentage of overlap between network masks and T2 lesion probability maps was calculated for each network at each study time-point.

Since correlation between brain networks has been shown to be driven primarily by low frequency fluctuations in blood-oxygen level dependent fMRI data, we detrended (linear, quadratic and cubic) and band-pass filtered (0.01-0.15 Hz)[12] the processed rIC time courses prior to computing static (sFNC) and dynamic functional network connectivity (dFNC).

Calculation of sliding-window dFNC correlation matrices. As suggested by Allen *et al.*,[8] dFNC between two rIC time courses was computed using a sliding window approach with a window size of 22 TR (66 s) in steps of 1 TR (i.e., 3 s). A rectangular window of 22 time-points convolved with a Gaussian of $\sigma=3\times TR$ was used for tapering along the edges. Covariance was estimated from the regularized inverse covariance matrix using the graphical LASSO framework.[2] We imposed an additional L1 norm constraint on the inverse covariance matrix to enforce sparsity, as described in detail elsewhere.[13] Finally, dFNC Pearson's correlation matrices computed for each subject were *r*-to-*z* Fisher transformed.

Calculation of dFNC dynamic connectivity properties. Once sliding-window dFNC matrices were obtained, dynamic connectivity properties were assessed using two approaches: the first was based on hard-clustering analysis,[8] and the second on the calculation of fuzzy meta-states.[14]

1. Hard-clustering analysis. Average connectivity patterns recurring during the experiment were identified using a clustering technique. Clustering was performed using a *k*-means algorithm, which partitions the data into a set of separate clusters to maximize the correlation within a cluster to the cluster centroid.[8] The selected optimal number of centroid states was 2, a number estimated using the elbow criterion, defined as the ratio of within-cluster to between-cluster distances. Average dwell times (the time that a subject spends in each FC state) and probability of transitioning from one state to another were also computed for each subject.[8]

2. Fuzzy meta-state analysis. Clustering analysis assumes that subjects are in a single connectivity state at a given time-point. A more flexible approach is to consider the possibility that multiple states (estimated using group temporal ICA) might be represented to varying degrees at the same time-point. The contribution of each state for a specific time is characterized by a vector that is called a *"meta-state"*.[15] Four global measures can be associated with these meta-states, and give an overall description of global connectivity dynamism: a) the number of times that subjects switch from one meta-state to another; b) the number of distinct meta-states that subjects occupy during

their scans; c) the range of meta-states subjects occupy; and d) the overall distance travelled by each subject through the state space.[15]

Calculation of between-group differences and changes over time of sFNC and dFNC strengths. Differences in sFNC and dFNC strength were represented using color-coded scales (red-yellow, blue-lightblue) according to the direction of the detected difference, as implemented in the GIFT MANCOVAN[4] and dFNC toolboxes, respectively.[8] Between-group comparisons of sFNC/dFNC were performed only on connections significantly correlated (or anticorrelated) at the one-sample *t* test in at least one group. In line with previous studies,[16] static and dynamic connectivity differences between groups were interpreted considering both the absolute strength and directionality of correlations between networks. In other words, even if encoded by the same color from the two-sample *t* test, increments of positive correlations were considered as connectivity increases, while reductions of negative correlations were considered as connectivity decreases. The same strategy was applied for interpreting increments of negative correlations and decrements of positive correlations, respectively.

Validation analyses. Dynamic RS FC techniques are relatively novel, and robustness of the results derived from such methodologies is still under debate. To test reliability of our results, ICA and dFNC were repeated by changing different settings, as described in the following paragraphs.

1. Balancing HC and CIS patients' groups by number of subjects. To test whether ICA estimation and between-group comparisons might be biased by the different sample size of HC and CIS patients, we split CIS patients in four sex- and age-matched subgroups, and concatenated data of each CIS subgroup, separately, with those of HC, to perform four ICA sub-analyses. Spatial similarity between components derived from the main ICA and those derived from the four ICA sub-analyses was measured by means of spatial correlation coefficient (using the FSL "fslcc" tool). Moreover, dynamic RS FC properties derived from the four CIS subgroups were compared with those of HC using the same statistical methodology applied to the main analysis.

2. Use of a data-driven number of group components to perform ICA.

The number of group ICs for the main ICA analysis was set to 100, to ensure comparability of dynamic FC results with previous studies.[8-11] However, since dFNC results may be influenced by the number of group independent components, we repeated ICA using the method included in GIFT (i.e., the minimum description length) to estimate the number of group components in our study cohort. This method gave us a median number of estimated components=57. Visual inspection of the spatial patterns and a frequency analysis of the spectra allowed to select 19 rICs, which were assigned to the following networks: sensorimotor (2 rICs), default mode network (DMN, 4 rICs), attention (3 rICs), executive (2 rICs), visual (4 rICs), temporal/auditory (3 rICs) and cerebellar (1 rICs) networks, as shown in **Supplementary Figure 1**.

Supplementary Results

sFNC analysis. When comparing CIS patients to HC, a baseline increase of sFNC was detected between the superior parietal cortices (DMN) and the bilateral cunei (visual network, p=0.009, corrected), as well as between the anterior cingulate cortex (DMN) and right fronto-parietal regions of the attention network (p=0.004, corrected). Conversely, left fronto-parietal regions of the attention network showed decreased sFNC with supplementary motor, secondary visual and temporal regions of sensorimotor and cognitive networks (p=range 0.004-0.04, corrected). Reduced sFNC tended to resolve over time, with the same comparison at year 2 showing increased sFNC between the anterior cingulate cortex (DMN) and the bilateral precentral gyri (p=0.01, corrected) and no significant sFNC decreases. Moreover, the paired *t* test showed significantly increased sFNC between the bilateral precunei and posterior cingulate cortices in the DMN (p=0.04, corrected) as well as between secondary visual regions and the cerebellum (p=0.04, corrected) in CIS patients at month 24 *vs* baseline. At uncorrected threshold, several inter-network sFNC increased connections and some reduced sFNC connections (mainly involving the attention, executive and visual networks) were observed at all time-points (raw data not shown, p=range <0.001-0.048) (**Figure 3**).

Between-group sFNC comparisons did not change substantially if non parametric tests were used (data not shown).

sFNC analysis according to type of disease onset showed that CIS patients had a baseline connectivity reduction mainly in those functional networks most affected by the clinical attack ($p<0.05$, uncorrected). These reductions tended to resolve over time. This occurred for example: 1) in the sensorimotor and cerebellar networks in patients experiencing a hemispheric or spinal cord onset; and 2) in the visual network in patients with an optic neuritis onset (**Supplementary Table 2**).

Validation analyses.

1.Balancing HC and CIS patients' groups by number of subjects. The main demographic and clinical characteristics, together with the main structural MRI and dFNC metrics calculated on the four CIS patients' subgroups are reported in **Supplementary Table 5.** All rICs identified by the main ICA analysis were present in the four ICA sub-analyses (spatial similarity ranging from r=0.30 to r=0.92). The comparison of dynamic FC properties between each CIS subgroup and HC was similar to that observed between all CIS patients and HC, although less statistically powerful. A main baseline reduction of State 1 dFNC and a baseline increase of State 2 dFNC were detected in all CIS subgroups *vs* HC (**Supplementary Figure 2),** while an overall increase in inter-network dFNC, mainly for the sensorimotor network and DMN, especially in State 2, was found in CIS patients *vs* HC at follow-up time-points (**Supplementary Figure 2**).

The fuzzy meta-state analysis showed similar global dynamism between subgroups of CIS patients and HC at baseline. A progressive increase of global dynamism was detected in almost all subgroups of CIS patients *vs* HC, with higher ranges and wider distances travelled through connectivity meta-states at month 12 and month 24 (**Supplementary Table 5**). The longitudinal analysis showed a progressive increase of global dynamism in CIS patients, mainly for subgroup 2 (number of meta-states at month 24 *vs* baseline p=0.005; number of changes between meta states at

month 24 *vs* baseline, p=0.04, range of meta-states occupied at month 24 *vs* baseline, p=0.03; total distance travelled through the state space, p=0.03).

2. Use of a data-driven number of group components to perform ICA.

The dFNC hard-clustering analysis on the 57 component-dataset indicated the presence of two different FC recurring states. The most recurrent state (frequency=65%) presented a relatively low strength of inter-network correlations, while the less recurrent state (frequency=35%) was characterized by relatively high inter-network correlation strengths (**Supplementary Figure 3**). Relatively high strengths of intra-network correlations were also observed in both states, mainly for the visual network (**Supplementary Figure 3**).

In line with the main analysis, the between-group comparison on this dataset showed: 1) reduced baseline inter- and intra-network connectivity in State 1 and increased inter-and intra-network FC in State 2 in CIS patients *vs* HC; and 2) a progressive increase of dynamic FC in both states at follow-up time-points, mainly in the sensorimotor network and in the DMN (**Supplementary Figure 3**).

The fuzzy meta-state analysis on this dataset was slightly less sensitive than that performed on the main dataset, since no changes over time in CIS patients were detected, nor significant differences in patients *vs* HC at baseline or at follow-up were found (**Supplementary Table 6**). However, a trend towards higher number of changes between meta-states was observed in CIS patients *vs* HC at month 24 (**Supplementary Table 6**).

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Supplementary Table 1. Percentage of T_2 lesions (derived from the average T_2 lesion probability map) located within the spatial patterns of relevant functional networks in patients with clinically isolated syndrome (CIS) at the different study time-points.

Functional network	**Percentage of T_2 lesions within relevant functional networks**		
	Baseline	**Month 12**	**Month 24**
Sensorimotor network	0.46 %	0.48 %	0.50 %
Default mode network	0.17 %	0.17 %	0.28 %
Attention network	0.08 %	0.04 %	0.05 %
Executive network	3.72 %	3.77 %	4.42 %
Visual network	1.09 %	1.74 %	1.86 %
Auditory network	0.24 %	0.25 %	0.65 %
Temporal network	0.30 %	0.59 %	0.47 %
Cerebellar network	0 %	0.01 %	0.06 %

Supplementary Table 2. Significant differences in static functional network connectivity (sFNC) in patients with clinically isolated syndrome (CIS) suggestive of multiple sclerosis, according to their type of onset, compared to healthy controls (HC). The network most affected by the demyelinating attack is taken as the reference for reporting connectivity strength: sensorimotor network (SMN) for patients with a hemispheric or spinal cord onset, and visual network (VIS) for patients with an optic nerve onset.

Time-point	**Relevant independent component (sensorimotor network)**	**Relevant independent component (belonging network)**	**Connectivity strength in HC**	**Connectivity strength in CIS patients with a hemispheric onset**	**p***
Baseline	Postcentral gyri (SMN)	Superior parietal/lingual/precuneus cortices (DMN)	-0.276	*-0.158*	0.042
	Postcentral gyri (SMN)	Middle temporal gyri (AUD)	0.099	**0.269**	0.018
Month 12	Right precentral gyrus (SMN)	ACC/caudate nuclei (EXE)	0.169	*0.053*	0.038
	Right precentral gyrus (SMN)	Left posterior lobes of the cerebellum (CER)	-0.205	*-0.088*	0.043
	Paracentral gyri (SMN)	Postcentral gyri (SMN)	0.035	**0.207**	0.001

	Paracentral gyri (SMN)	Middle/PCC (EXE)	0.075	**0.230**	0.010
	Paracentral gyri (SMN)	Middle cingulate cortex (EXE)	0.104	**0.235**	0.005
	Postcentral gyri (SMN)	Paracentral gyri (SMN)	0.035	**0.207**	0.001
	Postcentral gyri (SMN)	Posterior insular cortices (ATT)	0.220	*0.099*	0.021
	Postcentral gyri (SMN)	ACC/caudate nuclei (EXE)	0.107	*0.011*	0.008
Month 24	Precentral gyri (SMN)	Left precentral gyrus (SMN)	0.143	**0.344**	0.010
	Precentral gyri (SMN)	Postcentral gyri (SMN)	0.206	**0.484**	0.001
	Precentral gyri (SMN)	ACC/middle frontal cortices (DMN)	0.246	**0.474**	0.005
	Precentral gyri (SMN)	ACC/caudate nuclei (EXE)	0.170	*0.016*	0.010
	Precentral gyri (SMN)	Caudate nuclei (EXE)	0.165	*0.045*	0.027
	Right precentral gyrus (SMN)	ACC/middle frontal cortices (DMN)	0.261	**0.407**	0.012
	Paracentral gyri (SMN)	Middle/PCC (EXE)	0.069	**0.194**	0.009
	Paracentral gyri (SMN)	Middle cingulate cortex (EXE)	0.087	**0.194**	0.032
	Left precentral gyrus (SMN)	Precentral gyri (SMN)	0.143	**0.344**	0.010
	Left precentral gyrus (SMN)	Inferior parietal gyri/cunei (VIS)	0.069	**0.217**	0.046

	Left precentral gyrus (SMN)	Lingual gyri (VIS)	0.099	**0.259**	0.031
	Left precentral gyrus (SMN)	Middle temporal gyri (AUD)	0.017	**0.237**	0.002
	Postcentral gyri (SMN)	Precentral gyri (SMN)	0.206	**0.484**	0.001
	Postcentral gyri (SMN)	Inferior frontal/superior temporal/inferior parietal cortices (DMN)	-0.286	*-0.128*	0.038
	Postcentral gyri (SMN)	Superior parietal/lingual/precuneus cortices (DMN)	-0.209	*-0.057*	0.010
	Postcentral gyri (SMN)	Middle/PCC (EXE)	0.008	**0.135**	0.047
	Postcentral gyri (SMN)	Middle temporal gyri (AUD)	0.080	**0.281**	0.004
	Postcentral gyri (SMN)	Inferior temporal gyri (TMP)	0.165	*0.023*	0.025
	Postcentral gyri (SMN)	Anterior lobes of the cerebellum (CER)	-0.116	**-0.261**	0.030
Time-point	**Relevant independent component (visual network)**	**Relevant independent component (belonging network)**	**Connectivity strength in HCs**	**Connectivity strength in CIS patients with an optic nerve onset**	**p***

Baseline	Cunei (VIS)	Anterior insular cortices (EXE)	0.159	*0.001*	0.010
	Cunei (VIS)	Superior temporal gyri (AUD)	0.186	*0.039*	0.031
	Cunei (VIS)	Middle temporal gyri (AUD)	0.096	**0.207**	0.020
	Inferior parietal gyri/cunei (VIS)	Precunei (DMN)	0.388	**0.602**	0.025
	Inferior parietal gyri/cunei (VIS)	Inferior frontal/superior temporal/inferior parietal cortices (DMN)	0.228	*0.086*	0.042
	Inferior parietal gyri/cunei (VIS)	Superior parietal cortices/precunei (DMN)	0.104	**0.402**	0.001
	Inferior parietal gyri/cunei (VIS)	ACC (DMN)	0.204	*0.050*	0.037
	Inferior parietal gyri/cunei (VIS)	Left superior frontal/left superior parietal cortices (ATT)	-0.144	*-0.003*	0.024
	Inferior parietal gyri/cunei (VIS)	Middle cingulate cortex (EXE)	-0.274	*-0.184*	0.013
	Inferior parietal gyri/cunei (VIS)	Anterior lobes of the cerebellum (CER)	0.090	**0.296**	0.037
	Lingual gyri (VIS)	Right precentral gyrus (SMN)	0.268	*0.011*	0.027
	Lingual gyri (VIS)	Precunei (DMN)	0.311	*0.136*	0.011
	Superior cuneus cortices (VIS)	ACC (DMN)	0.211	*0.014*	0.025

Month 12	Middle occipital gyri (VIS)	Inferior temporal gyri (TMP)	0.034	**0.220**	0.024
	Inferior parietal gyri/cunei (VIS)	Precunei (DMN)	0.312	**0.533**	0.030
	Inferior parietal gyri/cunei (VIS)	Superior parietal cortices/precunei (DMN)	0.077	**0.345**	0.020
	Inferior parietal gyri/cunei (VIS)	Posterior insular cortices (ATT)	0.103	**0.308**	0.039
	Inferior parietal gyri/cunei (VIS)	Superior occipital gyri (VIS)	0.149	**0.364**	0.050
	Lingual gyri (VIS)	Superior parietal cortices/precunei (DMN)	0.077	**0.302**	0.016
	Lingual gyri (VIS)	ACC (DMN)	0.256	*0.033*	0.012
	Lingual gyri (VIS)	Middle/PCC (EXE)	-0.219	*-0.073*	0.045
	Superior cuneus cortices (VIS)	Superior parietal cortices/precunei (DMN)	0.226	**0.451**	0.010
	Superior cuneus cortices (VIS)	Anterior lobes of the cerebellum (CER)	0.049	**0.244**	0.043
	Superior occipital gyri (VIS)	Inferior parietal gyri/cunei (VIS)	0.149	**0.364**	0.050
Month 24	Middle occipital gyri (VIS)	Precunei (DMN)	0.230	**0.443**	0.017
	Cunei (VIS)	ACC/middle frontal cortices (DMN)	0.154	**0.274**	0.042
	Cunei (VIS)	Inferior frontal/superior temporal/inferior parietal cortices (DMN)	0.004	**0.157**	0.006

	Cunei (VIS)	Left superior frontal/left superior parietal cortices (ATT)	0.066	**0.182**	0.045
	Inferior parietal gyri/cunei (VIS)	Right precentral gyrus (SMN)	0.086	**0.237**	0.009
	Inferior parietal gyri/cunei (VIS)	Precunei (DMN)	0.394	**0.586**	0.043
	Inferior parietal gyri/cunei (VIS)	Superior parietal cortices/precunei (DMN)	0.119	**0.437**	0.004
	Lingual gyri (VIS)	Inferior frontal/superior temporal/inferior parietal cortices (DMN)	0.013	**0.165**	0.010
	Superior cuneus cortices (VIS)	Superior parietal cortices/precunei (DMN)	0.315	**0.443**	0.022
Time-point	**Relevant independent component (sensorimotor network)**	**Relevant independent component (belonging network)**	**Connectivity strength in HCs**	**Connectivity strength in CIS patients with a spinal cord onset**	**p***
Baseline	Left precentral gyrus (SMN)	Superior parietal/lingual/precuneus cortices (DMN)	0.192	*0.073*	0.017
	Left precentral gyrus (SMN)	Left superior frontal/left superior parietal	0.007	**0.115**	0.028

		cortices (ATT)			
Month 12	Precentral gyri (SMN)	Paracentral gyri (SMN)	0.258	**0.416**	0.010
	Precentral gyri (SMN)	Lingual gyri (VIS)	0.312	**0.459**	0.045
	Precentral gyri (SMN)	Middle temporal gyri (AUD)	0.326	**0.450**	0.047
	Right precentral gyrus (SMN)	Postcentral gyri (SMN)	0.180	**0.365**	0.010
	Right precentral gyrus (SMN)	ACC/middle frontal cortices (DMN)	0.270	**0.497**	0.028
	Right precentral gyrus (SMN)	Superior parietal cortices/precunei (DMN)	0.018	**0.187**	0.014
	Paracentral gyri (SMN)	Precentral gyri (SMN)	0.258	**0.416**	0.010
	Paracentral gyri (SMN)	Middle temporal gyri (AUD)	0.031	**0.212**	0.016
	Left precentral gyrus (SMN)	Lingual gyri (VIS)	0.105	**0.383**	0.003
	Postcentral gyri (SMN)	Right precentral gyrus (SMN)	0.180	**0.365**	0.010
Month 24	Precentral gyri (SMN)	ACC/middle frontal cortices (DMN)	0.246	**0.422**	0.009
	Right precentral gyrus (SMN)	ACC/middle frontal cortices (DMN)	0.261	**0.435**	0.014
	Left precentral gyrus (SMN)	ACC/caudate nuclei (EXE)	-0.028	**-0.240**	0.038
	Postcentral gyri (SMN)	Inferior frontal/superior temporal/inferior	-0.286	*-0.150*	0.025

		parietal cortices (DMN)			
	Postcentral gyri (SMN)	Right superior frontal/right superior parietal cortices (ATT)	0.006	**0.193**	0.009

*Two-sample t-test. Increased and reduced sFNC, in CIS patients compared to HCs, are highlighted in **bold** and *italics*, respectively.

Abbreviations: SMN=sensorimotor network; DMN=default-mode network; ATT=attention network; EXE=executive network; VIS=visual network; AUD=auditory network; TMP=temporal network; CER=cerebellar network; ACC=anterior cingulate cortex; PCC=posterior cingulate cortex.

Supplementary Table 3. Significant differences in dynamic functional network connectivity (dFNC) between healthy controls (HC) and patients with clinically isolated syndrome (CIS) suggestive of multiple sclerosis. The sensorimotor (SMN) and default-mode networks (DMN) are taken as the reference for reporting connectivity strength.

Time-point	**State**	**Relevant independent component (sensorimotor network)**	**Relevant independent component (belonging network)**	**Connectivity strength in HC**	**Connectivity strength in CIS patients**	**p[a]**	**p[b]**
Baseline	1	Left precentral gyrus (SMN)	Superior parietal/lingual/precuneus cortices (DMN)	0.107	*0.008*	0.004	0.003
		Paracentral gyri (SMN)	Right superior frontal/right superior parietal cortices (ATT)	-0.072	*-0.013*	0.036	0.037
		Right precentral gyrus (SMN)	Anterior insular cortices (EXE)	0.126	*0.055*	0.030	-
		Left precentral gyrus (SMN)	Middle occipital gyri (VIS)	0.032	**0.108**	0.036	-
		Precentral gyri (SMN)	Superior temporal gyri (AUD)	0.085	**0.157**	0.039	0.039

	2	Right precentral gyrus (SMN)	Postcentral gyri (SMN)	0.134	**0.250**	0.027	-
		Paracentral gyri (SMN)	Middle frontal/left inferior frontal/PCC/precuneus cortices (DMN)	0.028	**0.143**	0.039	0.048
		Precentral gyri (SMN)	Left superior frontal/left superior parietal cortices (ATT)	0.001	**0.120**	0.028	0.048
		Right precentral gyrus (SMN)	Left superior frontal/left superior parietal cortices (ATT)	0.010	**0.099**	0.008	0.009
		Left precentral gyrus (SMN)	Left superior frontal/left superior parietal cortices (ATT)	0.021	**0.092**	0.034	0.017
		Paracentral gyri (SMN)	Left putamen (EXE)	0.002	**0.116**	0.035	-
		Left precentral gyrus (SMN)	Superior occipital gyri (VIS)	0.076	**0.165**	0.031	-
Month 12	1	Paracentral gyri (SMN)	Postcentral gyri (SMN)	0.005	**0.097**	0.001	0.004
		Postcentral gyri (SMN)	Middle frontal/left inferior frontal/PCC/precuneus cortices	0.158	*0.096*	0.031	0.029

			(DMN)				
		Right precentral gyrus (SMN)	Superior frontal gyri (ATT)	0.119	*0.036*	0.049	0.038
		Precentral gyri (SMN)	Posterior insular cortices (ATT)	0.116	*0.024*	0.009	0.009
		Postcentral gyri (SMN)	Posterior insular cortices (ATT)	0.125	*0.056*	0.005	0.007
		Precentral gyri (SMN)	Anterior insular cortices (EXE)	0.086	*0.032*	0.025	0.027
		Right precentral gyrus (SMN)	Anterior insular cortices (EXE)	0.135	*0.067*	0.020	-
		Right precentral gyrus (SMN)	Caudate nuclei (EXE)	0.098	*0.021*	0.043	-
		Paracentral gyri (SMN)	Superior temporal gyri (AUD)	0.008	**0.082**	0.047	0.04
		Right precentral gyrus (SMN)	Left posterior lobes of the cerebellum (CER)	-0.122	*-0.027*	0.009	0.009
		Precentral gyri (SMN)	Anterior/central lobes of the cerebellum (CER)	-0.098	*-0.004*	0.013	0.023
	2	Paracentral gyri (SMN)	Postcentral gyri (SMN)	0.063	**0.166**	0.028	0.026
		Right precentral gyrus (SMN)	Superior parietal/PCC (DMN)	0.349	*0.270*	0.037	0.05
		Precentral gyri (SMN)	Superior parietal cortices/precunei	0.018	**0.152**	0.019	0.024

			(DMN)				
		Postcentral gyri (SMN)	Superior frontal gyri (ATT)	0.169	*0.043*	0.033	0.024
		Right precentral gyrus (SMN)	ACC/caudate nuclei (EXE)	0.133	*0.021*	0.038	0.038
		Postcentral gyri (SMN)	ACC/caudate nuclei (EXE)	0.113	*0.024*	0.025	0.05
		Postcentral gyri (SMN)	Lingual gyri (VIS)	0.047	**0.159**	0.047	0.026
Month 24	1	Paracentral gyri (SMN)	Left precentral gyrus (SMN)	0.065	**0.145**	0.037	0.04
		Precentral gyri (SMN)	Postcentral gyri (SMN)	0.075	**0.182**	0.028	0.008
		Paracentral gyri (SMN)	Superior parietal cortices/precunei (DMN)	-0.018	**0.062**	0.024	0.01
		Postcentral gyri (SMN)	Superior temporal gyri (AUD)	0.014	**0.119**	0.004	0.002
	2	Precentral gyri (SMN)	Right precentral gyri (SMN)	0.293	**0.395**	0.029	0.035
		Precentral gyri (SMN)	Paracentral gyri (SMN)	0.154	**0.286**	0.003^{+}	0.003
		Precentral gyri (SMN)	Left precentral gyrus (SMN)	0.153	**0.299**	0.012	0.016
		Paracentral gyri (SMN)	Left precentral gyrus (SMN)	0.101	**0.221**	0.011	0.012

		Precentral gyri (SMN)	Postcentral gyri (SMN)	0.167	**0.300**	0.030	0.043
		Precentral gyri (SMN)	ACC/Precunei (DMN)	0.192	**0.375**	<0.001^{+}	0.002^{+}
		Right precentral gyrus (SMN)	Precunei (DMN)	0.231	**0.336**	0.022	-
		Left precentral gyrus (SMN)	Precunei (DMN)	0.130	**0.235**	0.025	0.019
		Right precentral gyrus (SMN)	Left superior frontal/left superior parietal cortices (ATT)	-0.023	**0.316**	0.029	0.022
		Right precentral gyrus (SMN)	Middle/PCC (EXE)	0.098	*0.007*	0.031	-
		Right precentral gyrus (SMN)	Left putamen (EXE)	0.054	**0.167**	0.026	0.04
		Postcentral gyri (SMN)	Left putamen (EXE)	0.026	**0.113**	0.049	-
		Paracentral gyri (SMN)	Superior temporal gyri (AUD)	0.205	*0.162*	0.042	-
Time-point	**State**	**Relevant independent component (default-mode network)**	**Relevant independent component (belonging network)**	**Connectivity strength in HCs**	**Connectivity strength in CIS patients**	**p***	
Baseline	1	PCC/precunei (DMN)	Inferior frontal/superior temporal/inferior parietal cortices	0.036	**0.146**	0.005	0.003

	(DMN)				
ACC/middle frontal cortices (DMN)	Superior parietal cortices/precunei (DMN)	0.132	*0.050*	0.019	-
Precunei (DMN)	Middle frontal gyri (ATT)	0.168	*0.090*	0.030	-
Superior parietal/lingual cortices/precunei (DMN)	Left superior frontal/left superior parietal cortices (ATT)	-0.061	*0.033*	0.038	0.033
ACC/middle cingulate cortices (DMN)	Left superior frontal/left superior parietal cortices (ATT)	0.091	*-0.003*	0.003	0.011
Superior parietal cortices/precunei (DMN)	Middle frontal gyri (ATT)	0.158	*0.076*	0.016	0.013
Superior parietal cortices/precunei (DMN)	Left superior frontal/left superior parietal cortices (ATT)	0.173	*0.077*	0.008	0.008
Superior parietal cortices/precunei (DMN)	Inferior parietal gyri/cunei (VIS)	0.073	**0.186**	0.013	0.007
ACC (DMN)	Superior temporal gyri (AUD)	0.089	*0.003*	0.034	-

		Middle frontal/inferior frontal cortices/PCC/precunei (DMN)	Hippocampi (TMP)	-0.090	*0.009*	0.045	-
		Superior parietal cortices/precunei (DMN)	Hippocampi (TMP)	-0.100	*-0.026*	0.010	0.006
		ACC/middle frontal cortices (DMN)	Inferior temporal gyri (TMP)	0.109	*0.035*	0.025	-
		Superior parietal cortices/PCC (DMN)	Left posterior lobes of the cerebellum (CER)	-0.021	**0.061**	0.015	0.029
	2	Middle frontal/left inferior frontal cortices/PCC/precunei (DMN)	Superior parietal/lingual cortices/precunei (DMN)	0.096	**0.201**	0.015	0.013
		Precunei (DMN)	Left superior frontal/left superior parietal cortices (ATT)	0.027	**0.138**	0.032	-
		PCC/precunei (DMN)	Left superior frontal/left superior parietal cortices (ATT)	0.022	**0.131**	0.041	-
		Superior parietal/lingual	Left superior frontal/left superior	-0.008	**0.105**	0.017	0.004

cortices/precunei (DMN)	parietal cortices (ATT)				
ACC (DMN)	Left superior frontal/left superior parietal cortices (ATT)	-0.008	**0.106**	0.037	0.015
Middle frontal/left inferior frontal cortices/PCC/precunei (DMN)	Cunei (VIS)	0.062	**0.162**	0.033	-
Precunei (DMN)	Inferior parietal gyri/cunei (VIS)	0.252	**0.391**	0.006	0.021
Middle frontal/left inferior frontal cortices/PCC/precunei (DMN)	Inferior parietal gyri/cunei (VIS)	0.108	**0.216**	0.043	0.039
PCC/precunei (DMN)	Lingual gyri (VIS)	0.273	*0.125*	0.030	0.028
Superior parietal/lingual cortices/precunei (DMN)	Lingual gyri (VIS)	0.283	*0.178*	0.021	0.034
Middle frontal/left inferior frontal cortices/PCC/precunei (DMN)	Superior cuneus cortices (VIS)	0.085	**0.188**	0.031	0.028
ACC (DMN)	Superior temporal gyri (AUD)	0.361	*0.206*	0.007	0.011
Precunei (DMN)	Hippocampi (TMP)	-0.015	**0.134**	0.011	0.01

		Precunei (DMN)	Inferior temporal gyri (TMP)	0.070	**0.161**	0.030	0.039
		Precunei (DMN)	Left posterior lobes of the cerebellum (CER)	-0.181	*-0.015*	0.001^{+}	0.002^{+}
Month 12	1	Precunei (DMN)	PCC/precunei (DMN)	0.147	*0.074*	0.009	0.017
		ACC/middle frontal cortices (DMN)	Superior parietal/lingual cortices/precunei (DMN)	0.025	**0.090**	0.025	0.017
		Superior parietal cortices/PCC (DMN)	ACC/middle cingulate cortices (DMN)	0.054	**0.173**	0.014	0.019
		Superior parietal cortices/PCC (DMN)	Superior parietal cortices/precunei (DMN)	-0.007	**0.092**	0.023	0.047
		Superior parietal/lingual cortices/precunei (DMN)	Right superior frontal/right superior parietal cortices (ATT)	0.011	**0.105**	0.017	0.019
		Superior parietal cortices/precunei (DMN)	Left superior frontal/left superior parietal cortices (ATT)	0.236	*0.090*	<0.001	0.002
		ACC (DMN)	Left superior frontal/left superior	-0.111	*-0.004*	0.018	0.004

	parietal cortices (ATT)				
ACC (DMN)	Middle/PCC (EXE)	-0.064	*-0.009*	0.026	0.035
ACC/middle frontal cortices (DMN)	Cunei (VIS)	-0.005	**0.064**	0.041	-
Middle frontal/left inferior frontal cortices/PCC/precunei (DMN)	Inferior parietal gyri/cunei (VIS)	-0.005	**0.063**	0.016	-
Superior parietal cortices/precunei (DMN)	Inferior parietal gyri/cunei (VIS)	0.015	**0.147**	0.001	0.002
Inferior frontal/superior temporal/inferior parietal cortices (DMN)	Superior occipital gyri (VIS)	-0.128	*-0.022*	0.011	0.019
Superior parietal cortices/precunei (DMN)	Hippocampi (TMP)	-0.079	*0.014*	0.030	-
Middle frontal/left inferior frontal cortices/PCC/precunei (DMN)	Inferior temporal gyri (TMP)	0.183	*0.094*	0.016	0.045

		Superior parietal/lingual cortices/precunei (DMN)	Inferior temporal gyri (TMP)	-0.098	*0.033*	0.026	0.017
		Superior parietal cortices/precunei (DMN)	Inferior temporal gyri (TMP)	0.196	*0.118*	0.015	0.031
		ACC (DMN)	Anterior/central lobes of the cerebellum (CER)	-0.015	**0.074**	0.014	0.033
		ACC/middle frontal cortices (DMN)	Anterior lobes of the cerebellum (CER)	-0.132	*-0.071*	0.049	0.04
	2	ACC/middle frontal cortices (DMN)	Inferior frontal/superior temporal/inferior parietal cortices (DMN)	0.219	*0.136*	0.049	0.044
		Middle frontal/left inferior frontal cortices/PCC/precunei (DMN)	Superior parietal/lingual cortices/precunei (DMN)	0.083	**0.188**	0.027	0.005
		Middle frontal/left inferior frontal cortices/PCC/precunei (DMN)	Superior parietal cortices/precunei (DMN)	0.044	**0.155**	0.048	0.047

Inferior frontal/superior temporal/inferior parietal cortices (DMN)	Right superior frontal/right superior parietal cortices (ATT)	-0.016	**0.093**	0.037	-
Superior parietal/lingual cortices/precunei (DMN)	Right superior frontal/right superior parietal cortices (ATT)	0.029	**0.172**	0.038	-
Middle frontal/left inferior frontal cortices/PCC/precunei (DMN)	Superior frontal gyri (ATT)	0.169	*0.043*	0.002	0.008
ACC/middle cingulate cortices (DMN)	Left superior frontal/left superior parietal cortices (ATT)	0.022	**0.083**	0.008	0.035
Superior parietal cortices/PCC (DMN)	Right putamen (EXE)	-0.001	**0.119**	0.020	0.035
Superior parietal cortices/precunei (DMN)	Left putamen (EXE)	-0.021	**0.082**	0.044	-
Middle frontal/left inferior frontal cortices/PCC/precunei (DMN)	Inferior parietal gyri/cunei (VIS)	0.119	**0.204**	0.027	0.014

		Superior parietal/lingual cortices/precunei (DMN)	Inferior temporal gyri (TMP)	0.139	*0.084*	0.003	0.028
		Middle frontal/left inferior frontal cortices/PCC/precunei (DMN)	Left posterior lobes of the cerebellum (CER)	-0.211	*-0.090*	0.004	-
		Inferior frontal/superior temporal/inferior parietal cortices (DMN)	Left posterior lobes of the cerebellum (CER)	-0.153	*-0.055*	0.042	-
		Superior parietal cortices/PCC (DMN)	Left posterior lobes of the cerebellum (CER)	-0.154	*0.030*	0.002	0.024
		Superior parietal cortices/PCC (DMN)	Anterior/central lobes of the cerebellum (CER)	-0.189	*0.028*	<0.001	0.001
		Inferior frontal/superior temporal/inferior parietal cortices (DMN)	Anterior lobes of the cerebellum (CER)	-0.183	*-0.022*	0.003	0.005
		ACC (DMN)	Anterior lobes of the cerebellum	-0.252	*-0.105*	0.045	-

			(CER)				
Month 24	1	Inferior frontal/superior temporal/inferior parietal cortices (DMN)[Ω]	ACC/middle cingulate cortices (DMN)[Ω]	-0.258	*-0.164*	0.010	0.021
		Middle frontal/left inferior frontal cortices/PCC/precunei (DMN)[Ω]	ACC (DMN)[Ω]	-0.008	**0.082**	0.031	0.036
		Superior parietal/lingual cortices/precunei (DMN)	Right superior frontal/right superior parietal cortices (ATT)	-0.010	**0.107**	0.003	0.037
		PCC/precunei (DMN)	Left superior frontal/left superior parietal cortices (ATT)	-0.013	**0.051**	0.033	0.03
		Superior parietal cortices/PCC (DMN)[Ω]	Left superior frontal/left superior parietal cortices (ATT)[Ω]	-0.183	*-0.047*	<0.001	0.001
		Superior parietal/lingual cortices/precunei (DMN)	Left superior frontal/left superior parietal cortices (ATT)	0.091	*0.022*	0.004	0.002
		ACC (DMN)	Left superior frontal/left superior	0.090	*0.024*	0.007	0.015

			parietal cortices (ATT)				
		Superior parietal cortices/precunei (DMN)	Inferior parietal gyri/cunei (VIS)	0.050	**0.150**	0.038	0.017
		Middle frontal/left inferior frontal cortices/PCC/precunei (DMN)	Left posterior lobes of the cerebellum (CER)	-0.120	*-0.028*	0.022	0.023
		Middle frontal/left inferior frontal cortices/PCC/precunei (DMN) $^{\Omega}$	Posterior lobes of the cerebellum (CER) $^{\Omega}$	0.001	**0.080**	0.013	0.034
	2	Inferior frontal/superior temporal/inferior parietal cortices (DMN)	Superior parietal/lingual cortices/precunei (DMN)	0.101	**0.218**	0.024	0.012
		Inferior frontal/superior temporal/inferior parietal cortices (DMN)	ACC (DMN)	0.162	**0.265**	0.035	0.048
		ACC/middle frontal cortices (DMN)	Superior frontal gyri (ATT)	0.154	*0.040*	0.015	0.045

		Inferior frontal/superior temporal/inferior parietal cortices (DMN)	Caudate nuclei (EXE)	0.104	*0.007*	0.039	0.009
		ACC/middle frontal cortices (DMN)	Left putamen (EXE)	0.031	**0.207**	0.005	0.02
		Superior parietal cortices/PCC (DMN)	Left putamen (EXE)	-0.029	**0.082**	0.019	0.02
		ACC/middle cingulate cortices (DMN)	Cunei (VIS)	0.151	*0.052*	0.036	0.02
		Precunei (DMN)	Inferior parietal gyri/cunei (VIS)	0.266	**0.400**	0.011	0.004
		Superior parietal cortices/precunei (DMN)	Inferior parietal gyri/cunei (VIS)	0.126	**0.280**	0.036	0.033
		Precunei (DMN)	Inferior temporal gyri (TMP)	0.051	**0.175**	0.021	-

[a]Two-sample t-test; [b]Mann-Whitney U test. Increased and reduced dFNC in CIS patients compared to HCs, are highlighted in **bold** and *italics*, respectively. [Ω]significant time *x* group interactions in CIS patients *vs* HC. P values marked with [+] survive false discovery rate correction for multiple comparisons.

Abbreviations: SMN=sensorimotor network; DMN=default-mode network; ATT=attention network; EXE=executive network; VIS=visual network; AUD=auditory network; TMP=temporal network; CER=cerebellar network; ACC=anterior cingulate cortex; PCC=posterior cingulate cortex.

Supplementary Table 4. Significant differences in dynamic functional network connectivity (dFNC) in patients with clinically isolated syndrome (CIS) suggestive of multiple sclerosis, according to their type of onset, compared to healthy controls (HC). The network most affected by the demyelinating attack is taken as the reference for reporting connectivity strength: sensorimotor network (SMN) for patients with a hemispheric or spinal cord onset, and visual network (VIS) for patients with an optic nerve onset.

Time-point	**State**	**Relevant independent component (sensorimotor network)**	**Relevant independent component (belonging network)**	**Connectivity strength in HC**	**Connectivity strength in CIS patients with a hemispheric onset**	**p***
Baseline	1	Paracentral gyri (SMN)	Caudate nuclei (EXE)	0.077	*0.023*	0.050
		Left precentral gyrus (SMN)	Superior parietal/lingual/precuneus cortices (DMN)	0.108	*0.009*	0.019
		Postcentral gyri (SMN)	Middle temporal gyri (AUD)	0.047	**0.128**	0.042
	2	Precentral gyri (SMN)	Left superior frontal/left superior parietal cortices (ATT)	0.001	**0.129**	0.048

		Right precentral gyrus (SMN)	Postcentral gyri (SMN)	0.134	**0.295**	0.009
		Right precentral gyrus (SMN)	Anterior insular cortices (EXE)	0.232	*0.113*	0.039
		Postcentral gyri (SMN)	Right precentral gyrus (SMN)	0.134	**0.295**	0.009
Month 12	1	Precentral gyri (SMN)	Posterior insular cortices (ATT)	0.116	*0.023*	0.032
		Postcentral gyri (SMN)	Middle frontal/left inferior frontal/PCC/precuneus cortices (DMN)	0.158	*0.085*	0.014
		Postcentral gyri (SMN)	Posterior insular cortices (ATT)	0.124	*0.048*	0.012
	2	Precentral gyri (SMN)	Right precentral gyrus (SMN)	0.332	**0.415**	0.048
		Right precentral gyrus (SMN)	Precentral gyri (SMN)	0.332	**0.415**	0.048
		Paracentral gyri (SMN)	Postcentral gyri (SMN)	0.063	**0.188**	0.007
		Postcentral gyri (SMN)	Paracentral gyri (SMN)	0.063	**0.188**	0.007
		Postcentral gyri (SMN)	Posterior insular cortices (ATT)	0.200	*0.059*	0.031
		Postcentral gyri (SMN)	Middle cingulate cortex (EXE)	0.030	**0.153**	0.037
		Postcentral gyri (SMN)	Lingual gyri (VIS)	0.047	**0.167**	0.038

Month 24	1	Precentral gyri (SMN)	Postcentral gyri (SMN)	0.075	**0.245**	0.004
		Paracentral gyri (SMN)	Middle/PCC (EXE)	0.028	**0.108**	0.034
		Paracentral gyri (SMN)	Superior temporal gyri (AUD)	0.137	*0.052*	0.009
		Postcentral gyri (SMN)	Precentral gyri (SMN)	0.075	**0.245**	0.004
		Postcentral gyri (SMN)	Superior parietal/lingual/precuneus cortices (DMN)	-0.134	*-0.055*	0.04
		Postcentral gyri (SMN)	Middle temporal gyri (AUD)	0.013	**0.152**	<0.001
	2	Precentral gyri (SMN)	Right precentral gyrus (SMN)	0.293	**0.456**	0.003
		Precentral gyri (SMN)	Paracentral gyri (SMN)	0.154	**0.293**	0.017
		Precentral gyri (SMN)	Left precentral gyrus (SMN)	0.153	**0.333**	0.009
		Precentral gyri (SMN)	Postcentral gyri (SMN)	0.167	**0.375**	0.001
		Precentral gyri (SMN)	ACC/middle frontal cortices (DMN)	0.192	**0.389**	0.001
		Precentral gyri (SMN)	Left putamen (EXE)	0.114	**0.201**	0.033
		Right precentral gyrus (SMN)	Precentral gyri (SMN)	0.293	**0.456**	0.003
		Right precentral gyrus (SMN)	Postcentral gyri (SMN)	0.201	**0.320**	0.020

		Right precentral gyrus (SMN)	Left putamen (EXE)	0.054	**0.188**	0.027
		Paracentral gyri (SMN)	Precentral gyri (SMN)	0.154	**0.293**	0.017
		Left precentral gyrus (SMN)	Precentral gyri (SMN)	0.153	**0.333**	0.009
		Left precentral gyrus (SMN)	Postcentral gyri (SMN)	0.154	**0.256**	0.037
		Left precentral gyrus (SMN)	Inferior parietal gyri/cunei (VIS)	0.136	**0.238**	0.042
		Left precentral gyrus (SMN)	Middle temporal gyri (AUD)	0.130	**0.249**	0.024
		Left precentral gyrus (SMN)	Left posterior lobes of the cerebellum (CER)	-0.057	**-0.143**	0.04
		Postcentral gyri (SMN)	Precentral gyri (SMN)	0.167	**0.375**	0.001
		Postcentral gyri (SMN)	Right precentral gyrus (SMN)	0.201	**0.320**	0.02
		Postcentral gyri (SMN)	Left precentral gyrus (SMN)	0.154	**0.256**	0.03
		Postcentral gyri (SMN)	Left putamen (EXE)	0.026	**0.136**	0.048
		Postcentral gyri (SMN)	Lingual gyri (VIS)	0.149	**0.248**	0.014
		Postcentral gyri (SMN)	Middle temporal gyri (AUD)	0.137	**0.239**	0.045
Time-	**State**	**Relevant independent component**	**Relevant independent component**	**Connectivity**	**Connectivity**	**p***

point		**(visual network)**	**(belonging network)**	**strength in HCs**	**strength in CIS patients with an optic nerve onset**	
Baseline	1	-	-	-	-	-
	2	Cunei (VIS)	Right precentral gyrus (SMN)	0.191	*0.029*	0.038
		Inferior parietal gyri/cunei (VIS)	Anterior/middle cingulate cortices (DMN)	0.031	**0.176**	0.04
		Inferior parietal gyri/cunei (VIS)	Anterior/central lobes of the cerebellum (CER)	0.045	**0.212**	0.013
		Lingual gyri (VIS)	Precentral gyri (SMN)	0.342	*0.190*	0.044
		Lingual gyri (VIS)	Right precentral gyrus (SMN)	0.319	*0.127*	0.013
		Lingual gyri (VIS)	Precunei (DMN)	0.260	*0.116*	0.011
		Lingual gyri (VIS)	Superior parietal/lingual/precuneus cortices (DMN)	0.283	*0.145*	0.028
		Lingual gyri (VIS)	ACC (DMN)	0.278	*0.110*	0.041

		Lingual gyri (VIS)	Superior temporal gyri (AUD)	0.314	*0.157*	0.02
		Superior cuneus cortices (VIS)	Superior parietal/lingual/precuneus cortices (DMN)	0.389	*0.22*	0.034
		Superior cuneus cortices (VIS)	ACC (DMN)	0.264	*0.061*	0.033
		Superior occipital gyri (VIS)	Anterior/middle cingulate cortices (DMN)	0.01	**0.154**	0.013
		Superior occipital gyri (VIS)	Middle temporal gyri (AUD)	0.094	**0.323**	0.028
Month 12	1	Middle occipital gyri (VIS)	Cunei (VIS)	0.023	**0.137**	0.019
		Cunei (VIS)	Middle occipital gyri (VIS)	0.023	**0.137**	0.019
		Inferior parietal gyri/cunei (VIS)	PCC/precunei (DMN)	0.087	*0.029*	0.043
		Inferior parietal gyri/cunei (VIS)	Superior parietal cortices/precunei (DMN)	0.015	**0.165**	0.011
		Inferior parietal gyri/cunei (VIS)	Posterior insular cortices (ATT)	0.013	**0.181**	0.006
		Inferior parietal gyri/cunei (VIS)	Superior temporal gyri (AUD)	0.101	**0.194**	0.049
		Inferior parietal gyri/cunei (VIS)	Middle temporal gyri (AUD)	0.175	*0.085*	0.032

		Lingual gyri (VIS)	Superior parietal cortices/precunei (DMN)	0.032	**0.172**	0.037
		Superior cuneus cortices (VIS)	Superior parietal cortices/precunei (DMN)	0.114	**0.227**	0.033
		Superior occipital gyri (VIS)	Right superior frontal/right superior parietal cortices (ATT)	-0.011	**-0.124**	0.001
	2	Middle occipital gyri (VIS)	Inferior temporal gyri (TMP)	0.017	**0.223**	0.001
		Cunei (VIS)	Superior parietal cortices/precunei (DMN)	0.138	**0.316**	0.039
		Inferior parietal gyri/cunei (VIS)	Precunei (DMN)	0.300	**0.467**	0.004
		Inferior parietal gyri/cunei (VIS)	Middle frontal/left inferior frontal/PCC/precuneus cortices (DMN)	0.119	**0.236**	0.007
		Inferior parietal gyri/cunei (VIS)	Superior parietal cortices/precunei (DMN)	0.115	**0.388**	0.008

		Inferior parietal gyri/cunei (VIS)	Superior frontal gyri (ATT)	-0.057	**-0.198**	0.012
		Lingual gyri (VIS)	Postcentral gyri (SMN)	0.047	**0.202**	0.026
		Superior cuneus cortices (VIS)	Middle frontal/left inferior frontal/PCC/precuneus cortices (DMN)	0.136	**0.245**	0.031
		Superior cuneus cortices (VIS)	Superior parietal cortices/precunei (DMN)	0.258	**0.454**	0.014
		Superior cuneus cortices (VIS)	Superior frontal gyri (ATT)	-0.032	**-0.153**	0.014
		Superior cuneus cortices (VIS)	Superior temporal gyri (AUD)	0.280	**0.418**	0.017
Month 24	1	Middle occipital gyri (VIS)	Precunei (DMN)	0.114	**0.230**	0.026
		Cunei (VIS)	Left superior frontal/left superior parietal cortices (ATT)	0.007	**0.08**	0.016
		Cunei (VIS)	Anterior insular cortices (EXE)	0.098	*0.012*	0.031
		Inferior parietal gyri/cunei (VIS)	Right precentral gyrus (SMN)	0.011	**0.091**	0.044
		Inferior parietal gyri/cunei (VIS)	Superior parietal cortices/precunei	0.05	**0.218**	0.015

			(DMN)			
		Superior cuneus cortices (VIS)	Superior occipital gyri (VIS)	0.104	**0.185**	0.032
		Superior occipital gyri (VIS)	Superior cuneus cortices (VIS)	0.104	**0.185**	0.032
	2	Middle occipital gyri (VIS)	Right precentral gyrus (SMN)	0.072	**0.226**	0.043
		Middle occipital gyri (VIS)	Precunei (DMN)	0.172	**0.364**	0.015
		Middle occipital gyri (VIS)	Inferior frontal/superior temporal/inferior parietal cortices (DMN)	0.087	**0.190**	0.037
		Middle occipital gyri (VIS)	Inferior parietal gyri/cunei (VIS)	0.211	**0.376**	0.025
		Middle occipital gyri (VIS)	Superior cuneus cortices (VIS)	0.192	**0.487**	0.003
		Cunei (VIS)	Inferior frontal/superior temporal/inferior parietal cortices (DMN)	0.025	**0.159**	0.021
		Inferior parietal gyri/cunei (VIS)	Precunei (DMN)	0.266	**0.474**	0.002
		Inferior parietal gyri/cunei (VIS)	ACC/middle frontal cortices (DMN)	0.159	**0.284**	0.018

Inferior parietal gyri/cunei (VIS)	Inferior frontal/superior temporal/inferior parietal cortices (DMN)	0.076	**0.240**	0.010
Inferior parietal gyri/cunei (VIS)	Superior parietal cortices/precunei (DMN)	0.126	**0.384**	0.006
Inferior parietal gyri/cunei (VIS)	Left putamen (EXE)	0.105	**0.267**	0.027
Inferior parietal gyri/cunei (VIS)	Middle occipital gyri (VIS)	0.211	**0.376**	0.025
Inferior parietal gyri/cunei (VIS)	Superior cuneus cortices (VIS)	0.248	**0.424**	0.009
Inferior parietal gyri/cunei (VIS)	Anterior/central lobes of the cerebellum (CER)	0.106	**0.271**	0.026
Lingual gyri (VIS)	Inferior frontal/superior temporal/inferior parietal cortices (DMN)	0.051	**0.184**	0.007
Superior cuneus cortices (VIS)	Precunei (DMN)	0.322	**0.455**	0.033
Superior cuneus cortices (VIS)	Inferior frontal/superior	0.064	**0.219**	0.005

			temporal/inferior parietal cortices (DMN)			
		Superior cuneus cortices (VIS)	Middle occipital gyri (VIS)	0.192	**0.487**	0.003
		Superior cuneus cortices (VIS)	Inferior parietal gyri/cunei (VIS)	0.248	**0.424**	0.009
		Superior cuneus cortices (VIS)	Anterior/central lobes of the cerebellum (CER)	0.084	**0.258**	0.043
Time-point	**State**	**Relevant independent component (sensorimotor network)**	**Relevant independent component (belonging network)**	**Connectivity strength in HCs**	**Connectivity strength in CIS patients with a spinal cord onset**	**p***
Baseline	1	Paracentral gyri (SMN)	Precunei (DMN)	0.093	*0.021*	0.046
		Postcentral gyri (SMN)	PCC/precunei (DMN)	-0.063	**-0.173**	0.025
		Postcentral gyri (SMN)	Superior temporal gyri (AUD)	0.039	**0.160**	0.019
	2	Left precentral gyrus (SMN)	Postcentral gyri (SMN)	0.119	**0.288**	0.018
		Left precentral gyrus (SMN)	Superior parietal/lingual/precuneus	0.221	*0.083*	0.002

			cortices (DMN)			
		Left precentral gyrus (SMN)	ACC (DMN)	0.219	*0.028*	0.04
		Postcentral gyri (SMN)	Left precentral gyrus (SMN)	0.119	**0.288**	0.018
Month 12	1	Precentral gyri (SMN)	Paracentral gyri (SMN)	0.136	**0.264**	0.004
		Precentral gyri (SMN)	Lingual gyri (VIS)	0.149	**0.282**	0.008
		Precentral gyri (SMN)	Superior cuneus cortices (VIS)	0.033	**0.166**	0.038
		Right precentral gyrus (SMN)	Superior parietal cortices/precunei (DMN)	0.019	**0.118**	0.04
		Right precentral gyrus (SMN)	Left putamen (EXE)	0.038	**0.133**	0.047
		Right precentral gyrus (SMN)	Superior cuneus cortices (VIS)	0.080	**0.232**	0.014
		Paracentral gyri (SMN)	Precentral gyri (SMN)	0.136	**0.264**	0.004
		Paracentral gyri (SMN)	Middle cingulate cortex (EXE)	0.048	**0.124**	0.002
		Left precentral gyrus (SMN)	Lingual gyri (VIS)	0.031	**0.163**	0.02
		Postcentral gyri (SMN)	Middle cingulate cortex (EXE)	0.083	**0.178**	0.02
	2	Right precentral gyrus (SMN)	Precunei (DMN)	0.349	*0.206*	0.01

		Right precentral gyrus (SMN)	Inferior frontal/superior temporal/inferior parietal cortices (DMN)	0.162	*0.037*	0.048
		Left precentral gyrus (SMN)	Lingual gyri (VIS)	0.152	**0.307**	0.043
		Postcentral gyri (SMN)	Superior parietal cortices/precunei (DMN)	0.106	**0.229**	0.049
		Postcentral gyri (SMN)	Superior frontal gyri (ATT)	0.169	*0.021*	0.033
		Postcentral gyri (SMN)	Lingual gyri (VIS)	0.047	**0.182**	0.047
Month 24	1	Precentral gyri (SMN)	Anterior insular cortices (EXE)	0.032	**0.131**	0.025
		Right precentral gyrus (SMN)	Middle cingulate cortex (EXE)	0.026	**0.105**	0.012
		Paracentral gyri (SMN)	Left precentral gyrus (SMN)	0.065	**0.199**	0.014
		Paracentral gyri (SMN)	Middle cingulate cortex (EXE)	0.046	**0.127**	0.046
		Paracentral gyri (SMN)	Superior occipital gyri (VIS)	0.011	**0.123**	0.044
		Left precentral gyrus (SMN)	Paracentral gyri (SMN)	0.065	**0.199**	0.014
		Left precentral gyrus (SMN)	ACC/caudate nuclei (EXE)	-0.015	**-0.102**	0.031

		Postcentral gyri (SMN)	Hippocampi (TMP)	-0.084	**-0.190**	0.004
	2	Precentral gyri (SMN)	Paracentral gyri (SMN)	0.154	**0.336**	<0.001
		Precentral gyri (SMN)	ACC/middle frontal cortices (DMN)	0.192	**0.353**	0.034
		Paracentral gyri (SMN)	Precentral gyri (SMN)	0.154	**0.336**	0.001
		Paracentral gyri (SMN)	Left precentral gyrus (SMN)	0.101	**0.242**	0.033
		Paracentral gyri (SMN)	Middle cingulate cortex (EXE)	0.010	**0.143**	0.017
		Left precentral gyrus (SMN)	Paracentral gyri (SMN)	0.101	**0.242**	0.033
		Left precentral gyrus (SMN)	Middle frontal/left inferior frontal/PCC/precuneus cortices (DMN)	0.093	**0.228**	0.040
		Left precentral gyrus (SMN)	ACC/middle frontal cortices (DMN)	0.130	**0.265**	0.045

*Two-sample t-test. Increased and reduced dFNC, in CIS patients compared to HCs, are highlighted in **bold** and *italics*, respectively.

Abbreviations: SMN=sensorimotor network; DMN=default-mode network; ATT=attention network; EXE=executive network; VIS=visual network; AUD=auditory network; TMP=temporal network; CER=cerebellar network; ACC=anterior cingulate cortex; PCC=posterior cingulate cortex.

Supplementary Table 5. Demographic and structural MRI variables, together with mean dwell time (derived from the hard-clustering analysis) and measures of connectivity global dynamism (derived from the fuzzy meta-state analysis) in clinically isolated syndrome (CIS) patients, randomly divided into age- and sex-matched 4 subgroups. Results from healthy controls (HC) are also reported as reference for comparison.

	HC (n=13)	**CIS–1 (n=13)**	**CIS–2 (n=12)**	**CIS–3 (n=13)**	**CIS–4 (n=12)**	**p^a**	**p^b**	**p^c**	**p^d**
Demographic, clinical and structural MRI variables									
Gender (Male/Female)	9/4	8/5	7/5	8/5	7/5	0.76	0.65	0.76	0.65
Mean age (SD) (years) at baseline	33.1 (7.8)	30.5 (8.6)	31.2 (7.8)	30.3 (7.6)	30.6 (8.5)	0.2	0.27	0.1	0.35
Median baseline EDSS (range)	-	2.0 (0.0-3.0)	1.5 (0.0-2.5)	1.5 (1.0-3.0)	2.0 (1.0-2.0)	-	-	-	-
Mean baseline NBV (SD) (ml)	1506 (93)	1492 (94)	1523 (49)	1505 (92)	1466 (66)	0.8	0.5	0.9	0.3
Mean baseline T_2 LV (SD) (ml)	-	3.1 (2.9)	3.6 (4.4)	2.7 (3.5)	4.7 (5.6)	-	-	-	-
Mean baseline T_1 LV (SD)	-	3.2 (1.9)	2.2 (2.6)	1.3 (1.8)	3.3 (3.9)	-	-	-	-

(ml)									
Mean PBVC at year 2 *vs* baseline (SD)	-0.67 (0.88)	-0.81 (0.88)	-0.73 (0.89)	-0.43 (0.91)	-1.33 (0.95)	0.9	0.9	0.4	0.07
dFNC variables - Baseline									
Mean dwell time in dFNC – State 1 [windows] (SD)	84.9 (69.1)	70.7 (60.1)	81.4 (75.9)	93.1 (64.4)	84.1 (74.9)	0.7	0.7	0.6	0.7
Mean dwell time in dFNC – State 2 [windows] (SD)	17.2 (22.4)	18.7 (12.7)	32 (48.5)	15.1 (20)	39.3 (52.9)	0.3	0.7	0.8	0.3
Mean number of meta-states (SD)	17.5 (5.4)	23.6 (7.9)	16.2 (5.4)	19.5 (9)	17.7 (8.3)	**0.04**	0.5	0.65	0.9
Mean number of changes between meta-states (SD)	37.5 (10.2)	39.9 (9.1)	35.5 (7.2)	35.4 (10.2)	35.1 (11.1)	0.4	0.7	0.8	0.9
Mean range of meta-states occupied (SD)	9.6 (1.9)	10.8 (2.6)	9.3 (7.2)	9.2 (3.1)	10.3 (2.5)	0.2	0.9	0.8	0.4
Mean total distance travelled through the state-	46.6 (14.6)	54.8 (14.1)	44.8 (12.1)	45.1 (17.6)	46.2 (16.3)	0.1	0.9	0.8	0.9

space (SD)									
dFNC variables - Year 1									
Mean dwell time in dFNC – State 1 [windows] (SD)	102.3 (66.9)	101.5 (72.8)	70.4 (67.2)	61 (71.5)	73 (76.1)	0.7	0.2	0.1	0.2
Mean dwell time in dFNC – State 2 [windows] (SD)	13.2 (12.8)	20.3 (25.4)	17.5 (14.6)	46 (61.3)	22.5 (17.2)	0.7	0.5	0.1	0.2
Mean number of meta-states (SD)	17.8 (7.4)	20.1 (8.3)	21.4 (7.5)	17.2 (5.4)	21.4 (6.7)	0.5	0.2	0.9	0.3
Mean number of changes between meta-states (SD)	36.2 (10.6)	37.8 (8)	39.9 (9.6)	35.4 (8.4)	39.8 (9.8)	0.6	0.5	0.9	0.4
Mean range of meta-states occupied (SD)	8.8 (2.7)	9.9 (3.1)	10.3 (2.3)	9.4 (2.4)	11.3 (9.8)	0.4	0.2	0.4	**0.026**
Mean total distance travelled through the state-space (SD)	45.4 (17.2)	47.3 (12.4)	52.5 (13)	44.5 (12.2)	56 (13.9)	0.8	0.3	0.9	0.1
dFNC variables - Year 2									

Mean dwell time in dFNC – State 1 [windows] (SD)	92.7 (73.3)	74.5 (63.2)	74.4 (65.1)	97.7 (78.7)	58.7 (60.1)	0.5	0.8	0.9	0.3
Mean dwell time in dFNC – State 2 [windows] (SD)	13.2 (14.7)	25.1 (21.1)	19.6 (19.1)	22.2 (26.1)	22.8 (15.7)	0.2	0.7	0.6	0.2
Mean number of meta-states (SD)	18.5 (5.4)	23.2 (5.8)	22.1 (4)	18.7 (5.9)	22.1 (7.5)	**0.039**	0.08	0.7	0.087
Mean number of changes between meta-states (SD)	36.5 (8.8)	44.1 (6.5)	40.9 (7.1)	36.7 (9.8)	40.8 (11.2)	**0.026**	0.1	0.9	0.6
Mean range of meta-states occupied (SD)	9.2 (2.2)	11.3 (2.5)	11.5 (2.4)	9.4 (2.7)	11.3 (2.6)	**0.034**	**0.019**	0.7	**0.05**
Mean total distance travelled through the state-space (SD)	46.1 (12.0)	59.5 (10.8)	55.7 (12.9)	47.6 (15.4)	56.5 (18.7)	**0.004**	0.09	0.8	0.3

Mann-Whitney-U test in [a]CIS-1 *vs* HC, [b]CIS-2 *vs* HC, [c]CIS-3 *vs* HC and [d]CIS-4 *vs* HC. Abbreviations: SD=standard deviation; EDSS=Expanded Disability Status scale; LV=lesion volume; NBV=normalized brain volume; PBVC=percentage of brain volume change; dFNC=dynamic functional network connectivity.

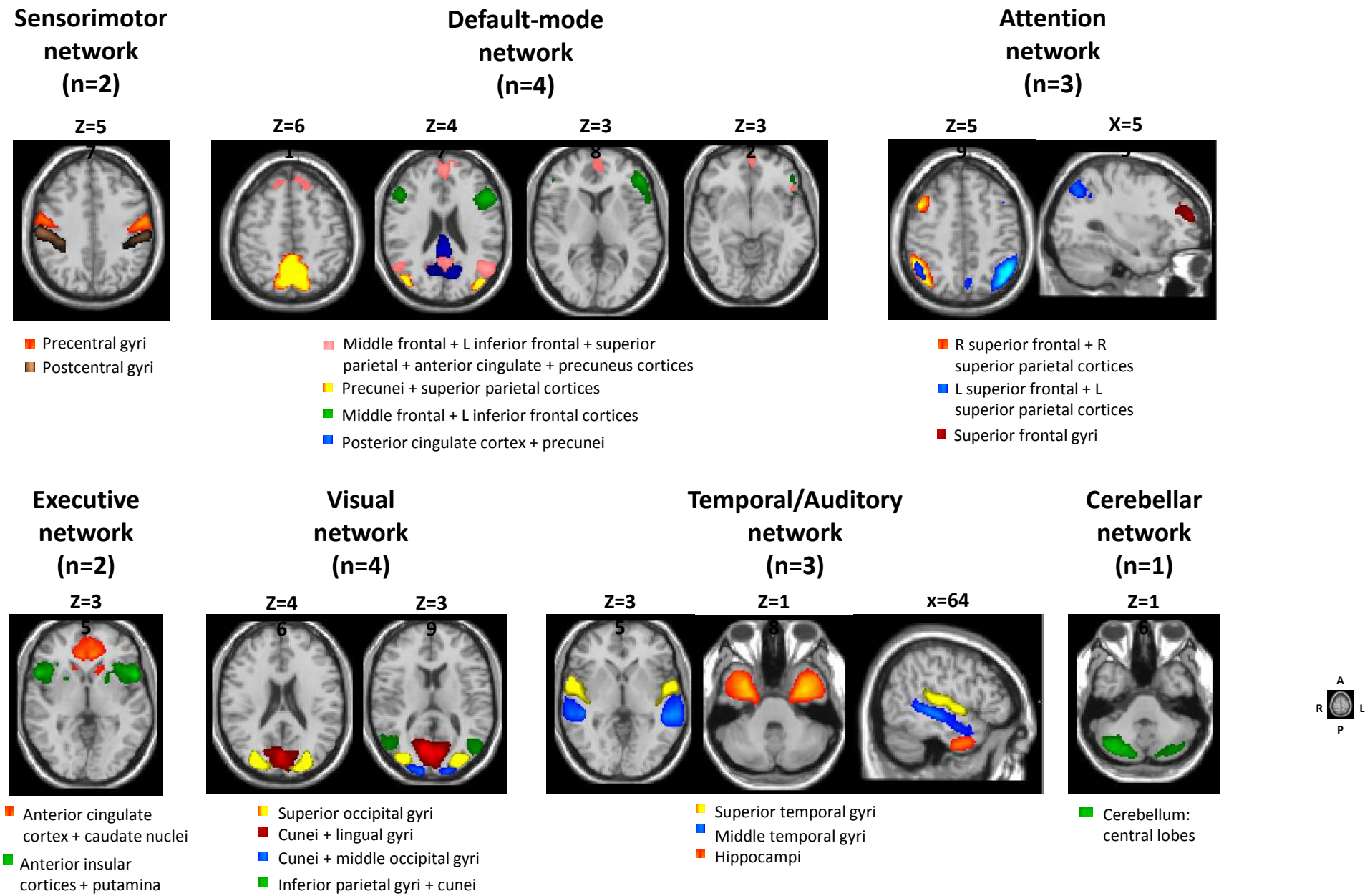
Supplementary Table 6. Mean dwell time (derived from the hard-clustering analysis) and measures of connectivity global dynamism (derived from the fuzzy meta-state analysis) in healthy controls (HC) and clinically isolated syndrome (CIS) patients at the different study time-points, obtained in the n=57 group independent components validation dataset. Mean values and standard deviations are reported for each measure.

	HC	**CIS**	**p**[a]
Baseline			
Mean dwell time in dFNC – State 1 [windows] (SD)	98.9 (76.4)	74.7 (65.4)	0.5
Mean dwell time in dFNC – State 2 [windows] (SD)	24 (42.8)	23 (29.5)	0.5
Mean number of meta-states (SD)	23.4 (5.6)	23.7 (7.3)	0.7
Mean number of changes between meta-states (SD)	43.5 (6.4)	42.5 (8.3)	0.8
Mean range of meta-states occupied (SD)	10.8 (2)	11.2 (2.3)	0.5
Mean total distance travelled through the state-space (SD)	55.5 (10.5)	58.7 (15.1)	0.6
Year 1			
Mean dwell time in dFNC – State 1 [windows] (SD)	106.6 (73.5)	66.2 (25.2)	0.1
Mean dwell time in dFNC – State 2 [windows] (SD)	14.2 (14.6)	25.2 (23.5)	0.1
Mean number of meta-states (SD)	22.5 (7.7)	25.6 (6.3)	0.2

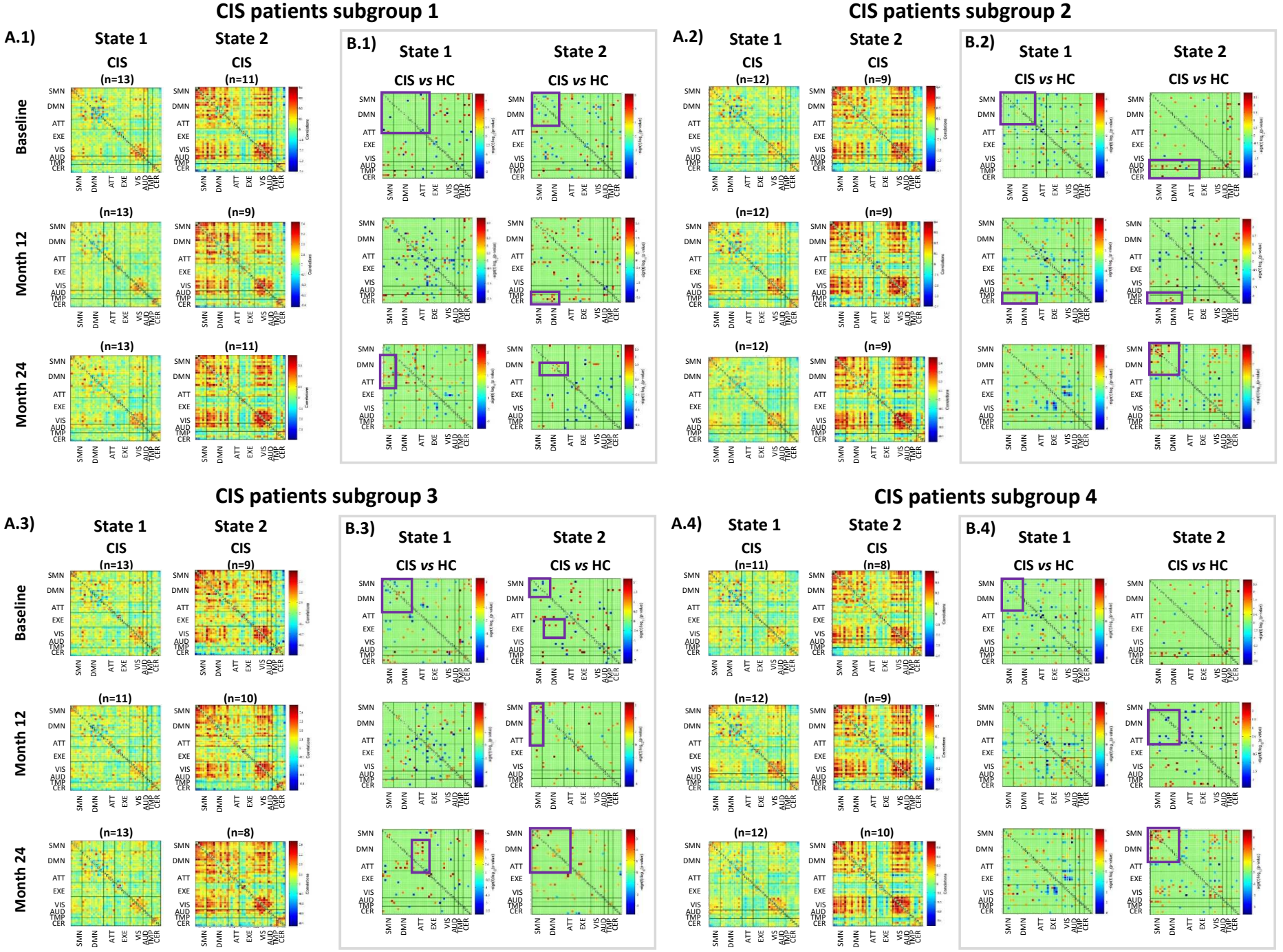
Mean number of changes between meta-states (SD)	42.4 (11.2)	44.1 (8)	0.6
Mean range of meta-states occupied (SD)	10.5 (3)	11.6 (1.9)	0.1
Mean total distance travelled through the state-space (SD)	55.2 (17.1)	60.9 (12.8)	0.1
Year 2			
Mean dwell time in dFNC – State 1 [windows] (SD)	64.2 (54.8)	56.8 (54.3)	0.4
Mean dwell time in dFNC – State 2 [windows] (SD)	18.2 (19.1)	25.6 (21.4)	0.1
Mean number of meta-states (SD)	25.5 (6.1)	24.7 (6.1)	0.8
Mean number of changes between meta-states (SD)	47 (7.5)	42.8 (7.4)	0.07
Mean range of meta-states occupied (SD)	11.5 (1.8)	11.8 (2.1)	0.5
Mean total distance travelled through the state-space (SD)	62.9 (12.4)	60.7 (13.5)	0.3

[a]Mann-Withney U test.

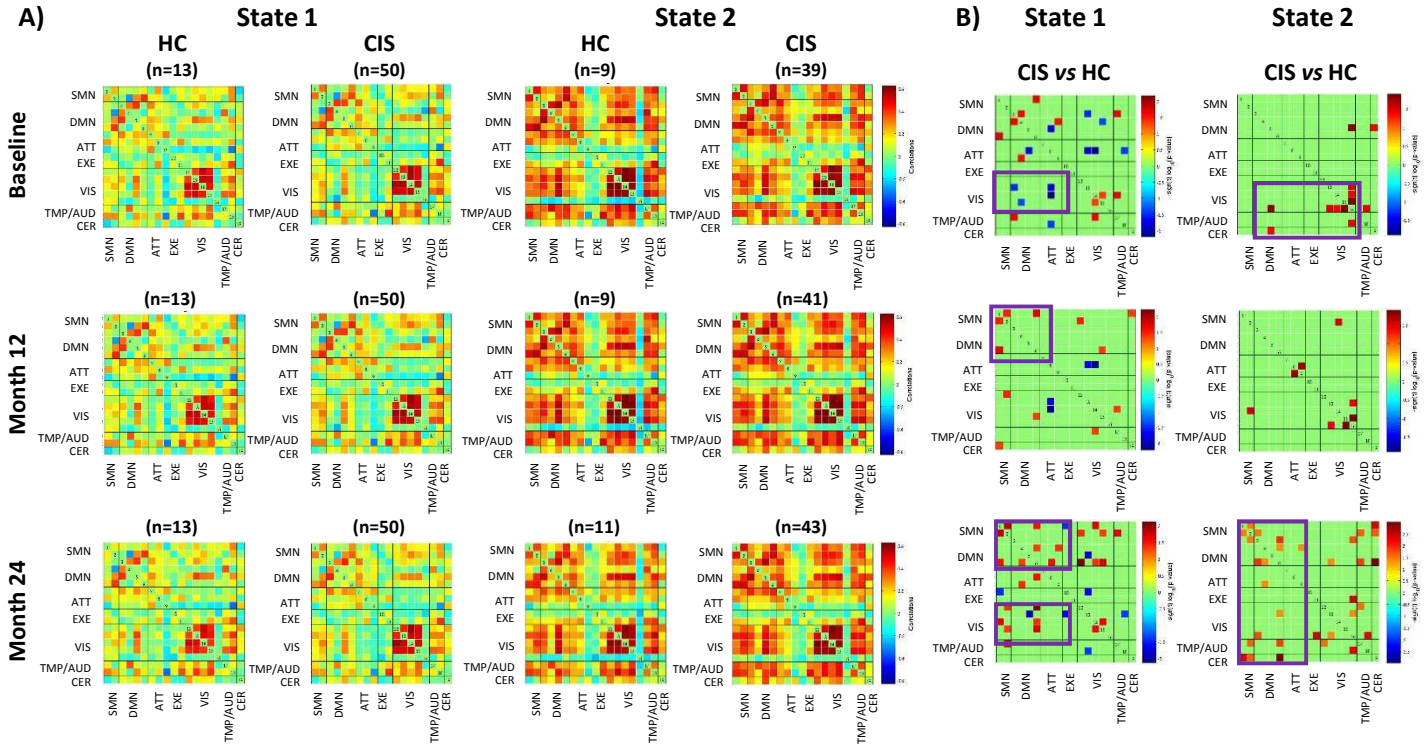
Abbreviations: dFNC=dynamic functional network connectivity; SD=standard deviation.



Supplementary Figure 1. Composite map of the 19 relevant independent components (rICs) obtained from the independent component analysis using n=57 as group components. rICs were sorted into seven subcategories: sensorimotor (2 components), default-mode (4), attention (3), executive (2), visual (4), temporal/auditory (3), and cerebellar (1) networks. Each colour in the composite map corresponds to a different rIC within a given subcategory. Images are presented in neurological convention. Abbreviations: A=anterior, P=posterior, R=right, L=left.



Supplementary Figure 2. Dynamic functional network connectivity (dFNC) analysis in clinically isolated syndrome (CIS) patients, divided in four age- and sex-matched subgroups vs healthy controls (HC): A.1, A.2, A.3, A.4) recurring connectivity states (State 1 and State 2) in HC and CIS patients' subgroups, at baseline, month 12 and month 24. Average dFNC connectivity strength between each pair of independent components (ICs) is colour-coded according to the intensity bar shown on the right (red: positive associations between ICs, blue: negative associations between ICs). **B.1, B2. B.3, B.4)** Comparisons of dFNC between HC and each CIS patients' subgroup ($p<0.05$, uncorrected, for illustrative purposes). Between-group differences are colour-coded according to their p value (colour intensity) and dFNC connectivity strength (red-yellow: higher positive dFNC [or lower negative dFNC] in CIS patients than in HC; blue: lower positive dFNC [or higher negative dFNC] in CIS patients than in HC). Violet boxes indicate between-group differences in dFNC. Abbreviations: n=number of subjects presenting the indicated state; SMN=sensorimotor network; DMN=default-mode network; ATT=attention network; EXE=executive network; VIS=visual network; AUD=auditory network; TMP=temporal network; CER=cerebellar network.



Supplementary Figure 3. Dynamic functional network connectivity (dFNC) analysis obtained from the independent component analysis using n=57 as group components: A) recurring connectivity states (State 1 and State 2) in healthy controls (HC) and clinically isolated syndrome (CIS) patients, at baseline, month 12 and month 24. Average dFNC connectivity strength between each pair of independent components (ICs) is colour-coded according to the intensity bar shown on the right (red: positive associations between ICs, blue: negative associations between ICs). **B)** Comparison of dFNC between CIS patients and HC ($p<0.05$, uncorrected, for illustrative purposes). Between-group differences are colour-coded according to their p value (colour intensity) and dFNC connectivity strength (red-yellow: higher positive dFNC [or lower negative dFNC] in CIS patients than in HC; blue: lower positive dFNC [or higher negative dFNC] in CIS patients than in HC). Violet boxes indicate between-group differences in dFNC. Abbreviations: n=number of subjects presenting the indicated state; SMN=sensorimotor network; DMN=default-mode network; ATT=attention network; EXE=executive network; VIS=visual network; TMP/AUD=auditory/temporal network; CER=cerebellar network.