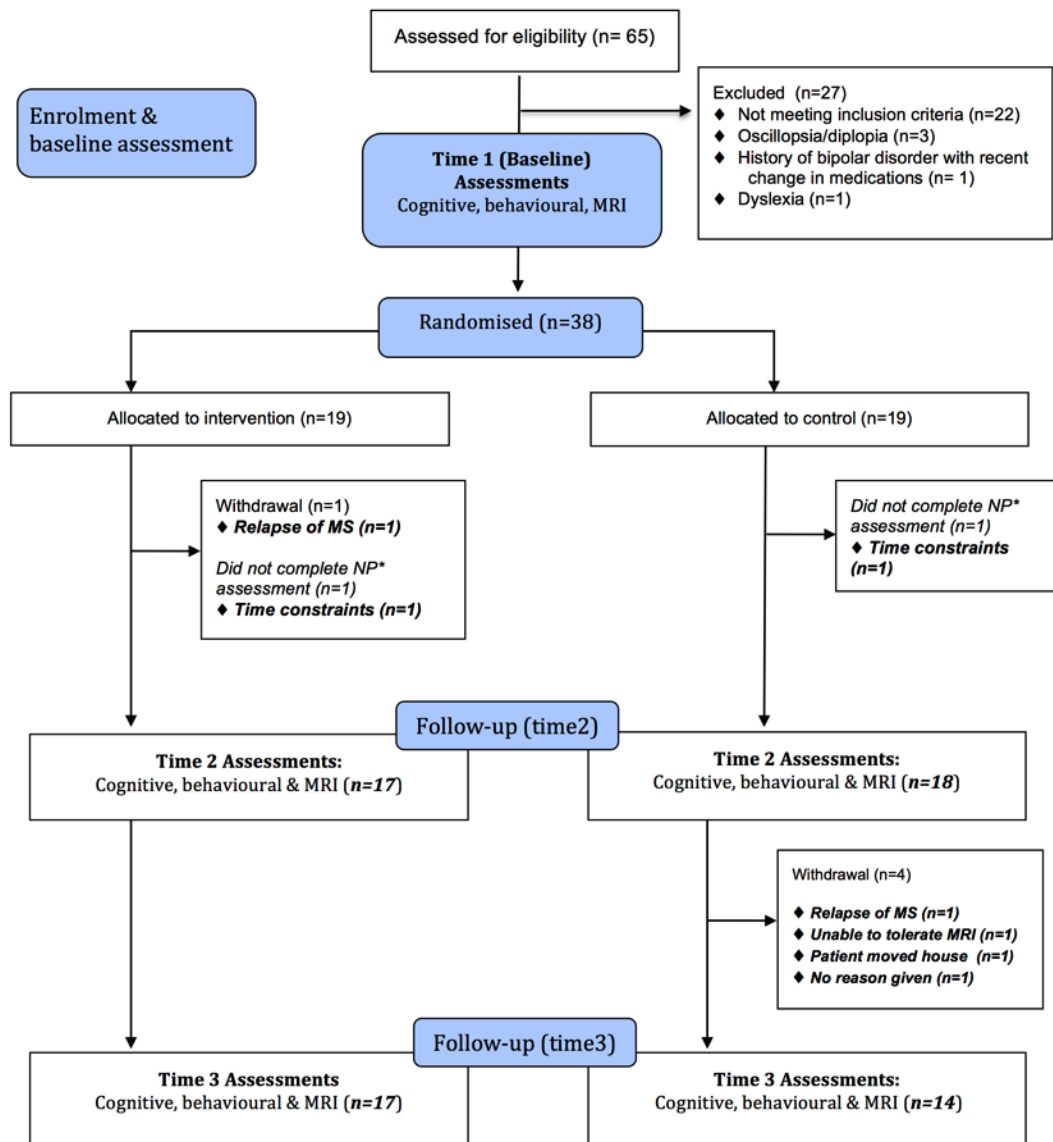


Supplemental materials

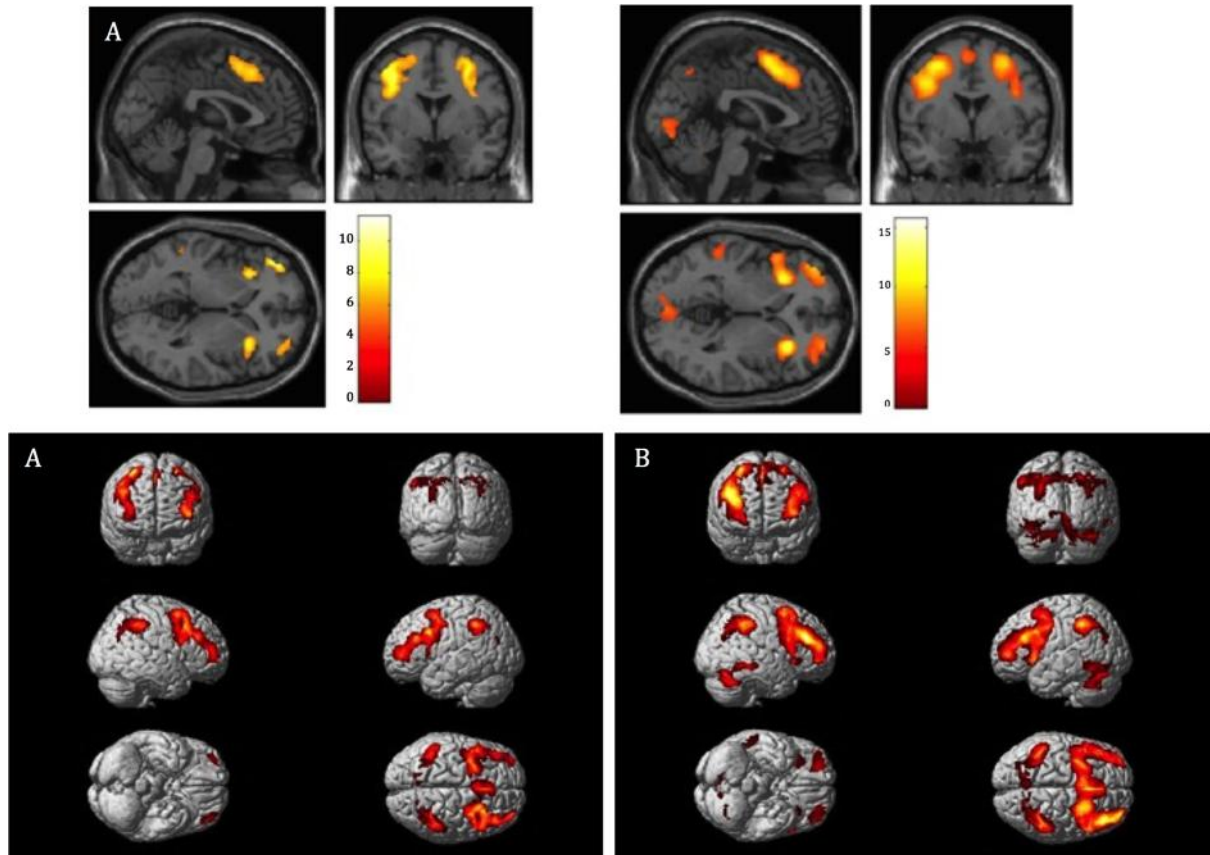
Supplementary figure 1 CONSORT flow diagram



*NP: neuropsychological

Supplemental material

Supplementary figure 2: Task main effects for all subjects



Task main effects for all subjects at baseline (n=38) showing areas of significant activation in: (a) 1-back, (b) 2-back ($p < 0.05_{\text{FWE corrected}}$).

Significant activation within prefrontal cortex (DLPFC), insula, inferior parietal lobules and occipital cortices.

Supplemental Table 2a:**Task Main effects for all subjects (baseline comparison):****Areas of Significant Activation ($p < 0.05$ FWE corrected) for 1-back > 0-back**

Brain region	<i>MNI Coordinates</i>			<i>Max t-score</i>	<i>K_e cluster</i>
	<i>x</i>	<i>y</i>	<i>z</i>		
<i>Dorsolateral prefrontal</i>					
Right middle frontal gyrus	28	8	58	11.49	4258
Left middle frontal gyrus	-40	48	2	9.6	
Left precentral gyrus	-36	0	42	9.6	3267
<i>Parietal (inferior parietal lobule)</i>					
Right angular gyrus	34	-56	44	11.21	
Right supramarginal gyrus	50	-40	42	10.82	1940
Left supramarginal gyrus	-44	-46	46	10.27	1528
<i>Occipital</i>					
Right superior occipital gyrus (lateral occipital cortex)	30	-64	38	11.56	1940
Left superior occipital gyrus (lateral occipital cortex)	-24	-64	44	9.43	1528
<i>Insula</i>					
Left insula	-30	22	2	8.54	147
Right insula	34	22	0	8.52	234
<i>Cerebellum</i>					
Left Cerebellum (crus)	-26	-64	-30	7.6	210
Right Cerebellum (crus)	30	-62	-32	7.51	344

Supplemental Table 2b:

Task Main effects for all subjects (baseline comparison):

Areas of Significant Baseline Activation ($p < 0.05$ FWE corrected) for 2-back>0 back task

Brain region	MNI Coordinates			Max <i>t</i> -score	<i>K_e</i> cluster
	<i>x</i>	<i>y</i>	<i>z</i>		
<i>Dorsolateral prefrontal</i>					
Right middle frontal gyrus	44	34	28	15.72	25383
Left inferior frontal gyrus (pars triangularis)	-46	30	28	12.72	
<i>Lateral Parietal (inferior parietal lobule)</i>					
Right supramarginal gyrus	40	-44	38	13.93	6009
Left supramarginal gyrus	-38	-44	40	13.57	
<i>Lateral Occipital</i>					
Left middle occipital gyrus	-26	-68	36	13.19	6009
Right occipital fusiform gyrus	38	-70	-20	8.83	
<i>Cerebellum</i>					
Left cerebellum	-26	-66	-30	11.56	3873
Right cerebellum	30	-64	-30	10.88	

Supplemental Table 3:

Baseline Quality of life and other behavioural measures

	Treatment group (n=19)		Control group (n=19)		<i>p</i>
	<i>Mean</i>	<i>± SD</i>	<i>Mean ±</i>	<i>± SD</i>	
FAMS	87.26	23.00	101.06	31.98	.170
PAM-13	59.52	18.42	64.26	15.65	.398
EQ5D	0.52	0.18	0.61	0.19	0.18
USE-MS	48.26	18.01	59.74	19.96	.270
MSNQ-S	36.89	13.49	34.68	11.51	.590
HADS-D	9.47	3.55	8.47	3.21	.507
HADS-A	9.26	3.72	9.37	5.56	.946
FSS	52.37	10.40	48.84	13.59	.375

FAMS Functional Assessment of MS, *MSNQ* Multiple Sclerosis Neuropsychological Questionnaire,

PAM-13, Patient Activation Measure *EQ-5D*, EuroQOL five dimension questionnaire

FSS Fatigue Severity Scale

USE-MS Unidimensional Self-Efficacy scale for MS,

HADS, Hospital Anxiety and Depression Scale (HADS-D = depression, HADS-A = anxiety subscale)

Supplemental Table 4: Quality of Life outcomes at follow up by treatment group.

<i>Scores at Time 1, Time 2 & Time 3</i>	Treatment (n=17)		Control (n=14)		<i>p</i>
	<i>Mean</i>	<i>± SD</i>	<i>Mean</i>	<i>± SD</i>	
FAMS 1	85.24	22.61	102.79	35.06	0.719
FAMS 2	82.18	25.09	99.14	36.89	
FAMS 3	89.00	30.99	101.00	32.40	
PAM-13 1	54.62	17.13	65.58	14.66	0.158
PAM-13 2	59.15	13.65	64.15	13.81	
PAM-13 3	58.79	15.52	62.10	15.90	
EQ-5D 1	0.49	0.13	0.61	0.22	0.388
EQ-5D 2	0.49	0.23	0.53	0.26	
EQ-5D 3	0.53	0.20	0.57	0.27	
MSNQ-S 1	35.65	13.56	34.79	12.34	0.892
MSNQ-S 2	32.76	13.81	31.36	15.83	
MSNQ-S 3	29.18	15.14	28.93	13.13	
HADS-D 1	9.82	3.38	9.21	3.38	0.921
HADS-D 2	9.82	3.34	9.50	4.35	
HADS-D 3	9.35	2.85	8.79	4.21	
HADS-A 1	9.18	3.80	9.86	5.74	0.334
HADS-A 2	9.29	4.47	8.21	5.06	
HADS-A 3	8.53	4.38	6.86	4.93	
FSS 1	52.12	10.89	49.43	14.18	0.912
FSS 2	52.53	13.21	48.57	15.64	
FSS 3	52.53	11.47	49.29	15.50	
USE-MS 1	16.00	5.85	19.00	6.72	0.996
USE-MS 2	15.76	5.62	18.69	6.60	
USE-MS 3	16.47	5.70	19.31	8.70	

FAMS: Functional Assessment of MS; PAM-13: Patient Activation Measure; EQ5D: EuroQOL five dimension questionnaire; USE-MS: Unidimensional Self-Efficacy scale for MS; MSNQ: Multiple Sclerosis Neuropsychological Questionnaire; HADS-D: Hospital Anxiety and Depression Scale (depression); HADS-A: Hospital Anxiety and Depression Scale (anxiety); FSS: Fatigue Severity Scale;

Supplemental Table 5: N-back error rate

<i>N-back Errors (Time 1, Time 2 & Time 3)</i>	Treatment (n=17)			Control (n=14)			<i>p</i>
	<i>Mean</i>	<i>SD</i>	<i>% error rate</i>	<i>Mean</i>	<i>SD</i>	<i>% error rate</i>	
0-back 1	3.24	3.419	5.14	3.71	4.92	5.89	.951
0-back 2	1.88	2.395	6.06	2.43	3.13	7.84	
0-back 3	2.53	3.642	8.16	2.64	2.50	8.52	
1-back 1	2.71	3.478	4.30	4.57	8.42	7.25	.270
1-back 2	1.47	2.183	4.74	1.86	1.61	6.00	
1-back 3	3.06	3.269	9.87	2.14	1.99	6.42	
2-back 1	5.24	4.816	8.32	6.00	9.83	9.52	.900
2-back 2	4.12	3.551	13.29	5.29	4.68	17.06	
2-back 3	4.76	5.761	15.35	5.29	3.83	17.06	

Appendix for MRI methodology

Hardware	
Field strength	1.5T
Manufacturer	Siemens
Model	Avanto
Coil type (e.g. head, surface)	32-channel head coil
Number of coil channels	32

Acquisition sequence	
Type (e.g. FLAIR, DIR, DTI, fMRI)	Dual echo TSE
Acquisition time	4 min
Orientation	Axial-oblique
Alignment (e.g. anterior commissure/poster commissure line)	Anterior commissure-posterior commissure (AC-PC)
Voxel size	0.898x0.898x5 mm ³
TR	3040ms
TE	11/ms
TI	N/A
Flip angle	150 degrees
NEX	2
Field of view	230x201mm ²
Matrix size	256x224
Parallel imaging	No
Cardiac gating	No
Contrast enhancement	No

Acquisition sequence	
Other parameters:	
ETL	6
Number of slices	33

Acquisition sequence	
Type (e.g. FLAIR, DIR, DTI, fMRI)	Task-based fMRI (ECHO planar imaging)
Acquisition time	3 runs (9 mins each)
Orientation	axial
Alignment (e.g. anterior commissure/poster commissure line)	AC-PC
TR	2520ms
TE	43ms
TI	
Flip angle	90
NEX	
Field of view	192x192mm ²
Matrix size	64x64
Parallel imaging	Yes
If used, parallel imaging method: (e.g. SENSE, GRAPPA)	GRAPPA, acceleration factor=2
Cardiac gating	No
Contrast enhancement	No

Acquisition sequence	
Type (e.g. FLAIR, DIR, DTI, fMRI)	MT-bSSFP
Acquisition time	12 volumes for a total duration of ~ 7minutes
Orientation	Axial oblique

Acquisition sequence	
Alignment (e.g. anterior commissure/poster commissure line)	AC-PC
Voxel size	0.93x0.93x5 mm ³
TR	Ranging from 3.66 to 5.96 ms
TE	=TR/2
TI	N/A
Flip angle	Ranging from 5 to 40 degrees
NEX	1
Field of view	240x180mm ²
Matrix size	256 x 96
Parallel imaging	No
Cardiac gating	No
Contrast enhancement	No