Abnormalities of the Executive Control Network in Multiple Sclerosis Phenotypes: An fMRI Effective Connectivity Study

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Abstract: The Stroop interference task is a cognitively demanding task of executive control, a cognitive ability that is often impaired in patients with multiple sclerosis (MS). The aim of this study was to compare effective connectivity patterns within a network of brain regions involved in the Stroop task performance between MS patients with three disease clinical phenotypes [relapsing-remitting (RRMS), benign (BMS), and secondary progressive (SPMS)] and healthy subjects. Effective connectivity analysis was performed on Stroop task data using a novel method based on causal Bayes networks. Compared with controls, MS phenotypes were slower at performing the task and had reduced performance accuracy during incongruent trials that required increased cognitive control. MS phenotypes also exhibited connectivity abnormalities reflected as weaker shared connections, presence of extra connections (i.e., connections absent in the HC connectivity pattern), connection reversal, and loss. In SPMS and the BMS groups but not in the RRMS group, extra connections were associated with deficits in the Stroop task performance. In the BMS group, the response time associated with correct responses during the congruent condition showed a positive correlation with the left posterior parietal → dorsal anterior cingulate connection. In the SPMS group, performance accuracy during the congruent condition

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showed a negative correlation with the right insula → left insula connection. No associations between extra connections and behavioral performance measures were observed in the RRMS group. These results suggest that, depending on the phenotype, patients with MS use different strategies when cognitive control demands are high and rely on different network connections. *Hum Brain Mapp* 37:2293–2304, 2016. © 2016 Wiley Periodicals, Inc.

Key words: effective connectivity; multiple sclerosis; phenotypes; Stroop; executive control; interference; fMRI; Bayes networks

INTRODUCTION

Cognitive deficits are observed in up to 65% of individuals with multiple sclerosis (MS) [e.g., Chiaravalloti and DeLuca, 2008]. Cognitive control is an important cognitive function that allows humans to respond appropriately to external stimuli, that is, select an appropriate action and suppress the inappropriate one. Cognitive control tasks in healthy individuals have been shown to engage a network of fronto-parietal regions as well as the basal ganglia [Dedovic et al., 2009; Kim et al., 2012; Leung et al., 2000; Roberts and Hall, 2008].

Neuroimaging evidence further shows that cognitive control tasks lead to aberrant patterns of cerebral activation in individuals with MS compared to healthy control subjects (HCs) [Bonnet et al., 2010; Parry et al., 2003; Smith et al., 2009]. Specifically, previous functional MRI (fMRI) studies showed that MS patients differ significantly in cerebral activation, and in patterns of functional and effective connectivity from HCs during tasks of working memory and cognitive control [Cader et al., 2009; Forn et al., 2012; Genova et al., 2009; Rocca et al., 2009, 2012]. While functional connectivity examines correlational information about the blood oxygen level dependent (BOLD) signal from brain regions, effective connectivity allows to examine how one brain region causes or influences activity in another brain region [Friston, 1994]. Differences in functional activation and connectivity observed in individuals with MS compared with HCs are thought to be due to the development of adaptive and maladaptive mechanisms in response to the accumulation of brain damage [Tomassini et al., 2012]. Further, functional activation and connectivity changes as well as cognitive deficits have been found to be more severe in advanced than in early MS phenotypes [Au Duong et al., 2005a; Audoin et al., 2007; Bester et al., 2013; Genova et al., 2013; Papadopoulou et al., 2013; Stojanovic-Radic and DeLuca, 2014].

One limitation of previous studies was that the approaches used to perform effective connectivity analysis (e.g., dynamic causal modeling [Rocca et al., 2009] or structural equation modeling (SEM) [Au Duong et al., 2005a,b; Audoin et al., 2007]) were based on methods requiring a priori specification of connections (i.e., it

should be hypothesized a priori if a connection between two regions exists or not), thus making an exhaustive search of the optimal data-driven connection model very difficult. Another limitation of SEM is that it is not specifically designed for multi-subject fMRI data processing, and requires pooling of time series across subjects [Jöreskog and van Thillo, 1972]. In this study, these methodological limitations were overcome by using the recently developed graphical analysis, based on causal Bayes networks proposed by Ramsey et al. [2010], which includes the Independent Multiple sample Greedy Equivalence Search (IMaGES), combined with the Linear non-gaussian Orientation, Fixed Structure (LOFS) [Ramsey et al., 2011]. This algorithm allows one to perform a fully data-driven effective connectivity analysis without any a priori assumptions about the presence or absence of a given connection between two regions, allowing the detection of network connections that can be otherwise missed.

Using such an approach, we performed an effective connectivity analysis on time series associated with Stroop task performance in HC and MS patients with three relapse-onset phenotypes [i.e., relapsing remitting (RRMS), benign (BMS), and secondary progressive (SPMS)]. Having the four groups allowed us to examine the HC pattern of connectivity associated with Stroop task performance as well as separate groups based on disease duration (BMS and SPMS groups have longer disease duration compared to the RRMS group) [Rovaris et al., 2009] and disability (RRMS and BMS groups have lower disability compared to the SPMS group) [Rovaris et al., 2009], as these factors might influence the pattern of effective connectivity. We hypothesized that, during a cognitive control task, in addition to performance deficits, all MS subjects would show connectivity abnormalities, including hyperconnectivity and interruption of information flow, compared with HC. In addition, we expected differences in connectivity patterns between the different MS phenotypes. Given previous findings of greater cognitive deficits and structural abnormalities [e.g., Bester et al., 2013; Genova et al., 2013; Stojanovic-Radic and DeLuca, 2014], we predicted that more connections will be observed in BMS and SPMS who have longer disease duration compared to RRMS.

TABLE I. Main average demographic, clinical, conventional MRI, and task performance characteristics of HC and patients with MS and different phenotypes enrolled in this study

	HC	RRMS	BMS	SPMS	<i>p</i> ^a
Age (years; SD)	38.1 (13.5)	37.4 (9.8)	41.2 (5.8)	46.1 (9.9)	0.001
Gender (M/F)	21/16	13/20	4/14	12/21	0.06 ^b
Education (years; SD)	–	13.16 (2.74)	10.88 (2.92)	11.52 (3.2)	0.06
Median EDSS (range)	–	2.0 (0.0–6.0)	2.0 (1.0–3.0)	6.0 (4.0–7.0)	<0.001 ^b
Disease duration (years; SD)	–	9.1 (6.2)	20.0 (4.3)	15.9 (7.6)	<0.001
T2 LV (ml; SD)	–	6.2 (7.5)	11.8 (10.5)	11.4 (9.2)	0.04
NBV (ml; SD)	1604.8 (100)	1536.5 (871)	1486.4 (102)	1446.7 (102)	<0.001
PASAT	–	35.42 (17.6)	36.52 (15.56)	26.55 (16.8)	0.06
Correct responses (congruent; %)	96.3 (5.1)	95.2 (6.8)	94.2 (7.8)	91.2 (12.1)	0.07
Correct responses (incongruent; %)	96.3 (5.4)	92.6 (10.5)	92.6 (8.1)	87.1 (10.7)	0.001
RT (congruent) [s]	0.84 (0.11)	0.90 (0.12)	0.98 (0.24)	1.00 (0.17)	<0.001
RT (incongruent) [s]	0.91 (0.12)	1.02 (0.15)	1.10 (0.24)	1.16 (0.16)	<0.001

^aANOVA model for group heterogeneity.

^bKruskall and Wallis test for group heterogeneity.

Abbreviations: RR: relapsing remitting; B: benign; SP: secondary progressive; SD: standard deviation; EDSS: expanded disability status scale; T2 LV: T2 lesion volume; NBV: normalized brain volume; RT: reaction time.

METHODS

Participants

Eighty-four individuals with MS [Polman et al., 2011] and 37 age- and gender-matched HCs participated in the study (Table I). Thirty-three patients had RRMS [Lublin and Reingold, 1996], 33 had SPMS [Lublin and Reingold, 1996] and 18 had BMS [defined as Expanded Disability Status scale (EDSS) score ≤ 3.0 and disease duration ≥ 15 years; Hawkins & McDonnell, 1999].

All research procedures compiled with the Code of Ethics of the World Medical Association (Declaration of Helsinki). The institutional review board approved the study and all subjects provided written informed consent before study participation.

At the time that the MRI was performed, all participants had been relapse- and steroid-free for at least three months. The inclusion criteria were (1) right-handedness; (2) absence of clinical involvement of the right upper limb (for MS subjects); (3) native Italian speaking; (4) ability to discriminate colors accurately; (5) normal or corrected-to-normal vision; (6) no concomitant therapy with antidepressants and psychoactive drugs; and (7) no history of major medical or psychiatric disorders.

MRI Acquisition

Using a 3.0 Tesla scanner (Philips, Best, The Netherlands), the following sequences of the brain were acquired from all study subjects: (a) dual echo turbo spin echo [repetition time (TR)/echo time (TE) = 3500/24–120 ms; echo train length = 5; flip angle = 150°, 44 contiguous slices, 3-mm-thick, axial slices, matrix size = 256 $\times$ 256, field of view (FOV) = 240 mm²]; (b) 3D T1-weighted fast field echo (TR/TE = 25/4.6 ms, flip angle = 30°, 220 contiguous, axial

slices, voxel size = 0.89 $\times$ 0.89 $\times$ 1 mm, matrix size = 256 $\times$ 256, FOV = 230 mm²); and (c) single-shot echo planar imaging (EPI) for fMRI acquisition (TR/TE = 2000/30 ms, flip angle = 85°, FOV = 240 mm², matrix = 128 $\times$ 128; slice thickness = 4 mm; 250 sets of 30 contiguous axial slices).

fMRI Paradigm

During fMRI, the modified version of the Stroop task, previously validated in HC and MS participants [Rocca et al., 2009, 2012], was used. The task was programmed with the Presentation software (www.neuro-bs.com, Version 0.70) and the stimuli were presented through a projector onto a rear projection screen. Participants viewed the screen through an angled mirror on the head coil. The Stroop task included three different trials: color-congruent trials (C; e.g., “red” printed in red), neutral trials (N; e.g., “dog” printed in red), and incongruent trials (I; e.g., “red” printed in green), separated by a fixation cross. Four colors and words (“rosso” [red], “blu” [blue], “giallo” [yellow], and “verde” [green]) were used in various combinations in the congruent and incongruent trials. The same colors were used during the neutral trial, in which the name of four different animals, selected to match the length and word frequency of color words, were presented (“ape” [bee], “gatto” [cat], “mucca” [cow], “anatra” [duck]). Each trial began with a fixation cross presented in the center of the screen for 2 s followed by the stimulus (a colored word) presented for 1.4 s. A variable interstimulus interval (range 600–7200 ms) was used. The number of stimuli for each condition was approximately the same, randomly selected within a range from 78 to 84 for each trial (C, I, and N).

Before performing the Stroop task in the scanner, all subjects had a short training session outside of the

TABLE II. List of ROIs activated during the Stroop interference task (full factorial model, $P < 0.001$ family wise error corrected for multiple comparisons) and selected as nodes for the effective connectivity analysis

ROIs	MNI space coordinate x	MNI space coordinate y	MNI space coordinate z
R VMPFC (BA 10)	13	55	0
L VMPFC (BA 10)	-13	55	0
dACC (BA 32)	2	3	50
R CN	11	4	5
L CN	-11	4	5
L INS (BA 13)	48	8	-1
R INS (BA 13)	-48	8	-1
PCC (BA 23)	1	-41	23
R PPL (BA 7)	31	-53	61
L PPL (BA 7)	-31	-53	61
R IFG (BA 47)	31	25	-24
L IFG (BA 47)	-31	25	-24
R DLPFC (BA 9)	26	38	42
L DLPFC (BA 9)	-26	38	42

Abbreviations: L: left; R: right; DLPFC: dorsolateral prefrontal cortex; VMPFC: ventromedial prefrontal cortex; PPL: posterior parietal lobule; dACC: dorsolateral anterior cingulate; CN: caudate nucleus; PCC: posterior cingulate cortex; INS: insula; IFG: inferior frontal gyrus.

scanner. Subjects were given standardized instructions to indicate the color of the ink in which the presented words were printed via an MRI compatible four-button response-box, held in their right hand. This device allowed recording accuracy of responses and reaction times (RT). All participants were instructed to respond as accurately as possible to the color of the ink the word was printed in and to ignore its meaning.

Structural MRI Analysis

Brain T2 lesion volume (LV) was quantified by one experienced observer, unaware of patient's identity, using a local thresholding segmentation technique (Jim 5, Xinapse Systems, Northants, UK). After the refilling of T1-hypointense lesions [Chard et al., 2010], normalized brain volume (NBV) was measured on 3D T1-weighted images, using the Structural Imaging Evaluation of Normalized Atrophy (SIENAX) software, included in FSL software library (version 4.1).

fMRI Analysis

fMRI data were analyzed using SPM8 software. Prior to statistical analysis, all images were realigned to the first scan, spatially normalized into the standard MNI space, and smoothed with a 10-mm, 3D-Gaussian filter. Subjects were included in the statistical analysis if they had a maximum translation/rotation lower than 3.0 mm in all directions. The goodness of normalization into the standard space was confirmed by the high correlation found between the normalized images and the default EPI template (r values ranging from 0.97 to 0.99).

Event-related responses for each condition were modeled using the general linear model and the theory of Gaussian fields [Friston et al., 1995], excluding trials on which individuals made an error. A first-level design matrix, including motion parameters as regressors, was built and specific effects were tested by applying appropriate linear contrasts on t statistical parametric maps (SPM_t). At this stage, hemodynamic changes during the congruent and incongruent conditions, as well as those related to the Stroop interference effect (incongruent vs. neutral), were defined. To determine commonly activated brain regions across the whole sample of subjects, a second level analysis was performed on the interference contrast (one-way ANOVA model, effects of interest, $P < 0.001$ family wise error corrected for multiple comparisons). Based on the second level results and on previous literature [Dedovic et al., 2009; Ridderinkhof et al., 2004b; Roberts and Hall, 2008], 14 regions of interest (ROI) were selected for effective connectivity analysis, as described in detail in the next section.

Effective Connectivity Analysis

Effective connectivity analysis was performed using the IMAges and the LOFS with Tetrad software (Version 5.6; <http://www.phil.cmu.edu/tetrad/>) [Ramsey et al., 2010, 2011]. This software uses causal Bayes network methods [Spirtes et al., 1993] to perform effective connectivity analysis on fMRI data, providing the direction of temporal influence among the regions within the network as well as the strength of the connection between regions. Since the method is search-based, there is no need of a predefined model of connections; and since the

search is constrained to predefined regions and penalized for overfitting, the risk of false-positive connections is minimized.

First, time series from the selected 14 ROI activated by the Stroop interference task (reported in Table II) were extracted from all study subjects. Then, time series from each study group (i.e., HC, RRMS, SPMS, and BMS, separately) were given as input to the IMaGES algorithm. This algorithm starts with an empty graph and searches forward, one new connection at a time, until it finds the set of connections that optimally represent the entire group of subjects. This is done by selecting the model having the highest Bayesian Information criterion (BIC) score across datasets. Since we were trying to estimate causal relationships among variables, “triangular” graphs (i.e., graphs where three regions are circularly connected, thus preventing the estimate of directional flow of information) were avoided by increasing the penalty function in the BIC score [Ramsey et al., 2010, 2011]. After that, IMaGES algorithm identified a directed acyclic graph for the set of regions, the LOFS algorithm [Ramsey et al., 2011] was used to determine the dominant direction (i.e., the causality) of the connection between two regions, thus eliminating bidirectional edges. Finally, after the connections were detected and oriented, a SEM estimator was used to calculate the goodness of fit of each dataset to the outcome connectivity model of the LOFS algorithm (see Supporting Information Figure). The parameter values of the SEM model (representing connection strengths for each study subject) were estimated by using a regression optimizer and were exported from Tetrad as t-scores for formal statistical analysis [Mills-Finnerty et al., 2014].

Statistical Analysis

Differences between groups of demographic, clinical, and structural MRI data were analyzed using ANOVA models and Kruskal and Wallis tests for continuous and categorical variables, respectively. Post-hoc tests were corrected for multiple-comparisons using Bonferroni correction. Repeated measures ANOVA with group (HC, RRMS, BMS, and SPMS) as a between-subject factor and trial type (correct congruent vs. correct incongruent trials) as a within-subject factor were used to compare behavioral measures (i.e., performance accuracy and RT). Age was included as a covariate in all analyses.

Effective connectivity coefficients estimated by SEM regression were averaged within each study group. Univariate ANOVA models adjusted for subjects' ages were performed to compare t-scores of effective connectivity coefficients between groups. Univariate correlations between t-scores of connectivity coefficients and behavioral variables were assessed using Spearman's correlation coefficient.

Figure 1.

A: Accuracy for the congruent and incongruent trials during the Stroop task. An ANOVA with group as a between-subject variable and trial type as a within-subject variable revealed a main effect of group ($P = 0.03$). **B:** RT for the congruent and incongruent trials during the Stroop task. A significant interaction ($P = 0.001$) and a main effect of group ($P < 0.0001$) was observed. ***indicates P -values < 0.0001 ; **indicates P -values < 0.005 ; * indicates P -values < 0.05 .

RESULTS

Clinical and Structural MRI Measures

Significant differences between groups in age, disease duration, and EDSS scores were found (Table I). Post-hoc comparisons showed that SPMS patients were significantly older ($P = 0.001$) and had longer disease duration ($P < 0.0001$) compared with RRMS ones. SPMS patients also had significantly higher EDSS scores than RRMS ($P < 0.0001$) and BMS ($P < 0.0001$) patients. No significant differences were observed in years of education and gender.

Significant differences between groups in T2 LV ($P = 0.04$) and NBV ($P = 0.001$) were also found. Post-hoc comparisons revealed that NBV was significantly lower in BMS ($P = 0.001$) and SPMS ($P < 0.0001$) compared with HC. SPMS patients had lower NBV than RRMS ones ($P = 0.001$).

TABLE III. Average connectivity values (together with their standard errors) of causal connections between brain regions observed in HC and patients with MS and different phenotypes during the performance of the Stroop task

Directed Connections	Average effective connectivity coefficients (SE)			
	HC	RRMS	BMS	SPMS
dACC=> R PPL	0.15 (0.03)	0.42 (0.07)*	–	0.18 (0.04)
L CN=>dACC	0.34 (0.05)	–	–	–
L CN=> R CN	0.71 (0.04)	0.73 (0.04)	0.71 (0.04)*	0.79 (0.04)*
L DLPFC=>dACC	–	–	0.29 (0.05)	–
L DLPFC=> R PPL	–	–	0.01 (0.03)	–
L INS=>dACC	–	0.25 (0.05)	–	–
L PPL=>dACC	–	–	0.51 (0.07)	–
L PPL=> R PPL	0.56 (0.03)	0.72 (0.04)	0.68 (0.04)	0.59 (0.05)
L VMPFC => L IFG	–	–	–	0.22 (0.06)
L VMPFC => L PPL	–	–	–0.18 (0.04)	–
L VMPFC =>PCC	–0.53 (0.07)	–0.43 (0.07)	–	–0.38 (0.08)
L VMPFC => R DLPFC	0.64 (0.04)	0.46 (0.04)	0.51 (0.05)*	0.62 (0.05)
L VMPFC =>R IFG	0.32 (0.04)	0.16 (0.04)	0.46 (0.05)	–
L VMPFC => R INS	–	0.14 (0.06)	0.11 (0.06)	–
L VMPFC=> R VMPFC	0.67 (0.03)	0.65 (0.04)	0.67 (0.03)	0.64 (0.04)
PCC=> L INS	–	–	0.27 (0.05)	0.29 (0.04)
PCC=> L PPL	0.41 (0.03)	0.31 (0.03)	0.32 (0.03)	–
PCC=> R PPL	–	–	–	0.16 (0.03)
R CN=>dACC	–	0.13 (0.04) ⁺	0.26 (0.05)	0.40 (0.05)
R DLPFC=>dACC	0.16 (0.05)	–	–	–
R DLPFC=> L DLPFC	0.78 (0.04)	0.59 (0.05)	0.71 (0.05)	0.63 (0.04)
R DLPFC=> L INS	0.15 (0.06)	–	0.04 (0.06)	–
R DLPFC=> R INS	0.28 (0.06)	–	–	0.30 (0.06)
R IFG=> L IFG	0.61 (0.04)	0.51 (0.04)*	0.55 (0.05)	0.60 (0.04)*
R INS=> L INS	–	–	0.37 (0.05)	0.34 (0.05)

Connections marked with * are reversed in patients compared with controls. The extra-connection (present in MS patients but not in controls) marked with + is reversed in relapsing remitting (RR) MS patients compared with BMS and SPMS.

Abbreviations: L: left; R: right; SE: standard error; DLPFC: dorsolateral prefrontal cortex; VMPFC: ventromedial prefrontal cortex; PPL: posterior parietal lobule; dACC: dorsolateral anterior cingulate cortex; CN: caudate nucleus; PCC: posterior cingulate cortex; IPL: inferior parietal lobule; INS: insula; IFG: inferior frontal gyrus.

There were no differences in NBV between the SPMS and BMS groups, or between the BMS and RRMS groups.

Behavioral Results During Stroop Performance

Accuracy

An ANOVA revealed a main effect of group ($P = 0.03$). Post-hoc independent samples t-test revealed that compared with HC, SPMS patients had significantly worse accuracy on congruent ($P = 0.02$) and incongruent ($P < 0.0001$) trials. SPMS patients' accuracy during incongruent trials was significantly worse compared with RRMS ($P = 0.04$). There were no accuracy differences between SPMS and BMS and between RRMS and BMS groups (Fig. 1a).

Reaction times

A significant interaction ($P = 0.001$) and a main effect of group ($P < 0.0001$) on RT was found. Post-hoc independent samples t-test revealed that compared with HC, RRMS patients had significantly slower RT on incongruent

($P = 0.02$) and congruent trials ($P = 0.001$). Similar findings were obtained for BMS (incongruent: $P = 0.004$; congruent: $P = 0.03$) and SPMS patients (incongruent: $P < 0.0001$; congruent: $P < 0.0001$; Fig. 1b). The SPMS group also had slower RT on incongruent ($P = 0.01$) and congruent ($P = 0.01$) trials than the RRMS group. The SPMS group was significantly slower than the BMS group on incongruent trials ($P = 0.02$) only. No RT differences were observed between RRMS and BMS groups.

Effective Connectivity Analysis

Within-group connectivity analysis

Table III and Figure 2 present effective connectivity patterns found during the Stroop task for the HCs and the three MS phenotypes, separately. There were six common connections detected across the four groups: (1) left posterior parietal lobule (PPL) => right PPL; (2) left ventromedial prefrontal cortex (VMPFC) => right VMPFC; (3) left VMPFC => right dorsolateral prefrontal cortex (DLPFC) (reversed in BMS vs. the other groups); (4) right DLPFC =>

Figure 2.

Effective connectivity graphs representing information flow during Stroop task performance for the HC, RRMS, BMS, and SPMS groups. VMPFC: ventromedial prefrontal cortex; DLPFC: dorso-lateral prefrontal cortex; dACC: dorsal anterior cingulate cortex; IFG: inferior frontal gyrus; INS: insula; CN: caudate nucleus; PCC: posterior cingulate cortex; PPL: posterior parietal lobule. Common connections appear in green. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

left DLPFC; (5) right inferior frontal gyrus (IFG) => left IFG (reversed in RRMS and SPMS vs. HC and BMS); and (6) left caudate nucleus => right caudate nucleus (reversed in BMS and SPMS vs. HC and RRMS; Figure 2 and Table III).

Healthy control

As expected, during the performance of this task, HC exhibited extensive communication between frontal areas that sent information to parietal areas. There were several interhemispheric connections, with regions in the left hemisphere exerting influence on homologous regions in the right hemisphere and vice versa. The left VMPFC and the right DLPFC had the greatest number of outgoing connections. Both regions exerted influence on four brain regions of the network and sent information to parietal regions through the dorsal anterior cingulate cortex (dACC) and posterior cingulate cortex (PCC; top-down information flow). The dACC received both top-down and

bottom-up information, i.e., from the right DLPFC and the left caudate nucleus, respectively.

Relapsing remitting multiple sclerosis

Abnormal connectivity patterns were found in each MS phenotype compared with HCs (Fig. 3). Connections from the right DLPFC to the dACC and the insula were lost in all three MS phenotypes as well as the connection between the left caudate nucleus and the dACC.

RRMS group lost three connections that were present in HCs and had two connections that reversed direction (Fig. 3a). There were also three extra connections compared with HCs and a left hemisphere dominance was observed in the connectivity pattern.

Benign multiple sclerosis

The BMS group lost five connections and had two connections that reversed direction compared with HCs. The

Figure 3.

A depiction of extra (red), reversed (yellow), and lost (gray) connections in the three groups of MS participants. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

BMS group had eight extra connections compared with HCs, primarily localized in the prefrontal cortex (Fig. 3b). Overall, connectivity pattern of the BMS group did not have a clear top-down information flow. While the PCC exerted influence on the left PPL and left insula, it did not receive any input from other regions. Both the left and right PPL received top-down influence from the left VMPFC and DLPFC, respectively.

Secondary progressive multiple sclerosis

The SPMS group lost four connections and had two connections that reversed direction compared to HC. The SPMS group had five extra connections, mainly between insula and posterior parietal regions. The VMPFC exerted influence over four other regions but without a clear top-down information flow.

Between group effective connectivity differences

The ANOVA on the six common connections revealed a significant group by connection strength interaction ($P < 0.0001$). Post-hoc independent samples t-test showed that RRMS patients had significantly weaker connection strength than HCs for the connection from the right to the left DLPFC ($P = 0.03$). BMS patients had significantly weaker connection strength than HC for the connection from the left to the right VMPFC ($P < 0.0001$). SPMS patients had significantly weaker connection strength than HCs for the connection from the left to the right VMPFC ($P = 0.01$) and between the left and right PPL ($P = 0.007$). BMS patients had significantly weaker connection strength than RRMS

and SPMS for the connection from the left to the right VMPFC ($P < 0.0001$). The right IFG $\Rightarrow$ left IFG connection, was significantly weaker in BMS compared with SPMS patients ($P = 0.05$). Compared with RRMS, SPMS patients had significantly weaker strengths of the connection from the left to the right PPL ($P = 0.001$) and stronger connection from the right to the left IFG ($P = 0.02$; see Table IV for a tabular representation of enhanced connections).

Effective Connectivity-Behavior Correlation

In HCs, several behavioral measures correlated with effective connectivity strengths. Specifically, connection strength from the dACC to the right PPL was negatively correlated with correct RT for both congruent and incongruent responses ($r = -0.51$, $P = 0.001$; $r = -0.43$, $P = 0.007$), as well as from the left VMPFC to the PCC ($r = -0.33$, $P = 0.05$; $r = -0.39$, $P = 0.02$). Connection

TABLE IV. List of shared causal connections showing differences in the impact of one region on the other between groups

Shared connections	
L PPL $\Rightarrow$ R PPL	HC > SPMS; RRMS > SPMS
L VMPFC $\Rightarrow$ R VMPFC	HC > BMS; HC > SPMS; RRMS > BMS; SPMS > BMS
R DLPFC $\Rightarrow$ L DLPFC	HC > RRMS
R IFG $\Rightarrow$ L IFG	SPMS > BMS; SPMS > RRMS
L CN $\Rightarrow$ R CN	–

strength from the dACC to the right PPL was negatively correlated with performance accuracy on correct congruent trials ($r = -0.34$, $P = 0.04$).

In MS phenotypes, significant correlations were found between behavioral measures and the strength of extra connections. In BMS patients, RT during correct congruent and incongruent trials was positively correlated with left PPL => dACC connection strength ($r = 0.52$, $P = 0.03$; $r = 0.51$, $P = 0.04$, respectively). In SPMS patients, the strength of the connection from the right to the left insula was negatively correlated with performance accuracy on congruent trials ($r = -0.41$, $P = 0.2$). There were no correlations between behavior and the strength of extra or reversed connections in RRMS patients.

DISCUSSION

The aim of the current study was to examine patterns of effective connectivity across three relapse-onset MS phenotypes (RRMS, BMS, SPMS) and how they compare to the HC connectivity pattern during performance of a cognitive control task (i.e., Stroop). Using IMAGES and LOFS algorithms, data-driven connection models were defined based on the time series acquired during the Stroop task performance. Behavioral results showed slower RT and reduced performance accuracy in all three MS phenotypes during the Stroop task relative to the HC group. Results also showed alterations in connectivity patterns and weaker frontal connections in all three MS phenotypes compared to HCs. Thus, the obtained results provide a detailed description of connectivity pattern alterations of the top-down processes thought to be involved in cognitive control in MS.

Connectivity pattern alterations

All MS phenotypes exhibited alterations of connectivity patterns compared with HCs. Such connectivity pattern alterations were of four types: (1) weak shared connections, (2) hyperconnectivity or presence of extra connections compared with HCs (independent of the number of extra connections), (3) reversal of the directionality of certain connections, and (4) loss of connections present in HCs.

The connectivity analysis revealed that MS patients and HCs shared six common connections: (1) left PPL => right PPL; (2) left VMPFC => right VMPFC; (3) left VMPFC => right DLPFC; (4) right DLPFC => left DLPFC; (5) right IFG => left IFG; and (6) left caudate nucleus => right caudate nucleus (Fig. 2 and Table III). All of these connections were interhemispheric, suggesting that they might play a role in cognitive control in terms of transferring information from one hemisphere to the other. The analysis of connection strengths suggests that three of the six connections were weaker in MS phenotypes than in HCs. Specifically, RRMS patients had weaker connectivity than the HCs between the right and left DLPFC; BMS and

SPMS patients had significantly weaker connectivity than the HCs between the left and the right VMPFC; and the SPMS patients had significantly weaker connectivity than the HCs between the left and right PPL. These frontal and parietal regions have been shown to play an important role in cognitive control [e.g., Ridderinkhof et al., 2004a,b; Roberts and Hall, 2008]. However, while MS patients exhibited alterations in shared connections, behavioral consequences were not observed. That is, we detected no correlation between the strengths of these weakened connections and behavioral measures, such as accuracy or RT. The absence of a correlation might be due to RT being a global measure of performance that is not captured by the connections discussed above. More research is needed to better understand the significance of shared connections.

We did observe a relationship between behavioral measures and extra connections in two of the studied MS phenotypes. Specifically, the significantly slower RT in the BMS group, as compared to the HCs, was correlated with the connection strength between the left PPL and dACC. This bottom-up connection (from the parietal to the frontal area) thus might be maladaptive [see Schoonheim et al., 2015] for other possible interpretations), as it is associated with slower response at both congruent and incongruent trials. However, performance accuracy of BMS patients was not significantly different from HCs. While no single connection showed an association with faster RT, the observed global hyperconnectivity might help maintain performance accuracy comparable to the HCs, but at the cost of RT. Indeed, BMS patients had the greatest number of alterations in the connectivity pattern (8 extra connections). Such interpretation of hyperconnectivity is in line with previous studies in MS [Leavitt et al., 2012] and other populations [e.g., Dobryakova et al., 2015; Hillary et al., 2015].

In SPMS patients, performance accuracy on congruent trials was correlated with the extra connection from the left to the right insula. Such a relationship is suggestive of the connection being maladaptive, since the increased influence of the right insula on the left insula was associated with worse performance accuracy.

While RRMS patients had slower RT than HC group, no relationship between altered connections and behavior was observed. This suggests that the altered connectivity pattern in RRMS patients may be adaptive, allowing for accurate performance. However, RRMS patients also had significantly longer RT, suggesting that performance accuracy was preserved with a consequence of a slowed RT. This result is consistent with a previous effective connectivity study [Leavitt et al., 2012], and in conjunction with the results from BMS, might suggest that as the disease duration increases, the extra connections become maladaptive and lead to both accuracy and RT deficits, as observed in BMS and SPMS, respectively. Indeed, the three MS phenotypes have distinct clinical features, with RRMS and BMS groups being similar in terms of having low

disability, while the BMS and SPMS groups being similar in terms of disease duration. The clinical profile of the phenotypes can potentially explain the presence/absence of the association between the behavioral and connectivity measures.

Lost connections could not be related to behavior parametrically as the connectivity algorithm does not provide connectivity strengths when a connection is absent. However, a consistent loss of connections can be observed in all MS phenotypes compared with HCs. Specifically, all MS groups lost a connection between the left caudate nucleus and the dACC and between the right DLPFC and the dACC. The dACC is a region that has been shown to play an important role in cognitive control [Cohen et al., 2000] and is often activated during cognitive control tasks such as the Stroop. Its primary role is considered to be conflict monitoring and error detection [Cohen et al., 2000; Harrison et al., 2005]. Consistent with this interpretation, the connectivity model in the HC group showed the dACC receiving both top-down information from the DLPFC and bottom-up information from the left caudate nucleus [Ridderinkhof et al., 2004b]. According to our findings, the interplay between these regions seems to be disrupted in all MS phenotypes and probably adds to the observed deficits in the Stroop task performance. The insula is another region commonly activated during cognitive control tasks [Dosenbach et al., 2006, 2008; Wager et al., 2005] and in the HC group the right DLPFC sent information to the insula, bilaterally. In all MS groups, the connection between the right DLPFC and the insula appears to be disrupted. Specifically, RRMS patients lost the right DLPFC => insula connection bilaterally; BMS patients lost the connection between the right DLPFC and the right insula; and SPMS patients lost the connection between the right DLPFC and the left insula. While the alterations of the right DLPFC-insula coupling differs between the three MS phenotypes, the loss of these connections might contribute to the observed deficits in the performance of the Stroop task.

All three MS phenotypes had two reversed connections. While no associations between behavioral measures and reversed connections were observed, in all MS groups the reversal of connections seems to disrupt the top-down information flow (connections that send information from the frontal to parietal areas) observed in the HC group. Additionally, reversed connections contributed to a switch in laterality (information transfer from the left to the right hemisphere; see yellow arrows in Fig. 3). Of note is the connection between the dACC and the right PPL that was reversed in RRMS patients. In the HC group, this connection was associated with faster RT. This association was absent in SPMS patients, while the connection itself was lost in BMS patients. A similar association was observed between the left VMPFC to PCC connection with RT in the HC group only. All MS phenotypes showed slower RT compared with HCs. While more research is necessary to

understand the relationship between reversal of connections and behavioral measures, we suggest that these connections might play an important role in efficient information processing during high cognitive control demands that the Stroop task exerts.

Limitations

In this study, a neuropsychological evaluation was not performed. Thus, there is a possibility that some of the MS patients were cognitively impaired. While being a limitation, this does not invalidate the current findings for several reasons. First, rather than examining connectivity differences between cognitively impaired and unimpaired participants, the aim of this study was to assess differences in causal influences between the regions involved during cognitive control between MS phenotypes and HCs, and within the three MS phenotypes. Additionally, the tests administered during a neuropsychological evaluation are different from the Stroop paradigm presented during the fMRI and might not translate into performance on the Stroop task. Future investigations should focus on differences within MS phenotypes with and without cognitive impairment.

Further, in this study we used a novel effective connectivity method. This approach allowed us to overcome certain limitations associated with causal inference from BOLD data [Ramsey et al., 2010]. However, this method has its own drawbacks. For instance, the existence of a given causal connection is first estimated at a group level and then reconstructed (together with its strength) at a single subject level. Therefore, grouping of study subjects becomes a particularly critical choice that can affect effective connectivity estimates. Moreover, a formal between-group comparison of causal connections strengths is possible only on common connections across groups. Thus, future studies are needed to replicate our findings.

Finally, we normalized EPI images to a template that was derived from healthy subjects' data. That might have caused the introduction of "spurious" voxels in the areas with severe brain atrophy. However, since we used the EPI template as a reference for normalization (with a relatively coarse spatial resolution), this effect should be tolerable.

CONCLUSIONS

This is the first study that explored differences in neural substrates associated with cognitive control between MS phenotypes and HCs, using an effective connectivity analysis with a completely data-driven approach. The three MS phenotypes exhibited deficits in the Stroop task performance and alterations of the associated connectivity pattern, characterized by hyperconnectivity, loss, and reversal of existing connections, as well as weakening of connections. Extra connections were associated with

specific performance deficits in BMS and SPMS, but not in RRMS patients. Such results suggest that extra connections may become maladaptive as the disease and disability progresses and the brain loses its ability to compensate. More importantly, the disparate connectivity patterns reflect that the three MS phenotypes used distinctive mechanisms during the Stroop task performance. Such information might help better understand cognitive control deficits in specific types of MS and potentially lead to the development of rehabilitation strategies that aid in cognitive control.

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