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Default Network Connectivity Is Linked to Memory Status in Multiple Sclerosis

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Abstract

Memory impairment affects 50% of multiple sclerosis (MS) patients. Altered resting-state functional connectivity (FC) has been observed in the default network (DN) of MS patients. No study to date has examined the association of DN FC to its behavioral concomitant, memory. The approach of the present study represents a methodological shift allowing straightforward interpretation of FC alterations in MS, as it presupposes specificity of a network to its paired cognitive function. We examined FC from fMRI collected during rest in the DN of 43 MS patients with and without memory-impairment. Memory-intact patients showed increased DN FC relative to memory-impaired patients. There were no regions of higher FC in memory-impaired patients. DN FC was positively correlated with memory function, such that higher FC was associated with better memory performance. Results were unchanged after controlling for cognitive efficiency, supporting specificity of the DN to memory and not cognitive status more generally. These findings support DN FC as a marker of memory function in MS patients that can be targeted by future treatment interventions. Pairing a functional network with its behavioral concomitant represents a straightforward method for interpreting FC alterations in patients with MS. (*JINS*, 2014, *20*, 937–944)

Keywords: Multiple sclerosis, Memory, Default network, Functional connectivity, fMRI, Cognition

INTRODUCTION

Approximately 50% of patients with multiple sclerosis (MS) experience memory impairment (Thornton and Raz, 1997). MS is a chronic inflammatory disease resulting in white matter lesions (Lucchinetti et al., 2000) and brain atrophy (Anderson et al., 2010; Benedict et al., 2009; Bermel et al., 2006; Chard et al., 2009; Fisher et al., 2008). Atrophy is particularly prominent within the brain's chief memory structure (Squire et al., 2004), the hippocampus (Anderson et al., 2010; Benedict et al., 2009;). Patients experience hippocampal atrophy and related memory decline after only 5 years of relapsing-remitting MS (Anderson et al., 2010; Sicotte et al., 2008). However, MS-related structural abnormalities in the brain (i.e., atrophy) only account for 10–15% of the variance in memory performance in persons with MS (Benedict, Cookfair, et al., 2006; Benedict et al., 2004; Christodoulou et al., 2003; Sanfilipo et al., 2006). As a result, the field has looked to functional neuroimaging as a tool to identify neurophysiological markers related to cognitive decline. Resting-state functional connectivity (FC) is one such marker that has captured the attention of researchers, with a burgeoning literature showing abnormal FC within large-scale neuronal networks including the default network (DN) of patients with MS (Hawellek et al., 2011; Rocca et al., 2010, 2012; Roosendaal et al., 2010). The DN consists of limbic structures associated with memory (hippocampus, anterior cingulate cortex, posterior cingulate cortex; Greicius, Krasnow, Reiss, & Menon, 2003) and overlaps functionally with the autobiographical memory network (Spreng, Mar, & Kim, 2009). In addition, DN FC is reduced in memory-impaired populations (i.e., Alzheimer's disease) (Greicius, Srivastava, Reiss, & Menon, 2004). And, DN FC changes have consistently been noted in clinical samples characterized by memory decline (Bai et al., 2008; Rombouts, Barkhof, Goekoop, Stam, & Scheltens, 2005; Sorg et al., 2007; Wang et al., 2006). Taken together, mounting evidence

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supports the role of the DN as a primary memory network of the brain. It is, therefore, somewhat surprising that no study to date has evaluated the association of DN FC to memory status in patients with MS. Here, we investigate DN FC among MS patients with and without memory impairment. We assess FC within a preselected network of interest (DN) in the context of its related function (memory) by placing a single seed in posterior cingulate cortex (PCC), the most critical hub of the DN (Greicius et al., 2003). We expect MS patients with memory impairment to demonstrate lower DN FC relative to MS patients without memory impairment, consistent with findings in other memory-impaired populations.

MATERIAL AND METHODS

Subject Enrollment

Participants were 43 MS patients (33 RRMS, 4 PPMS, 6 SPMS; 6 males) with no exacerbations in the last 4 weeks, no current corticosteroid use, and no history of psychiatric illness or other neurologic condition. Mean age of the sample was 45.9 ± 9.4 years; mean disease duration was 10.5 ± 5.8 years.

Standard Protocol Approvals, Registrations, and Patient Consents

Institutional review boards responsible for ethical standards at UMDNJ and the Kessler Foundation Research Center approved this study. Written informed consent was obtained from all subjects before participation. All research was completed in accordance with the Helsinki Declaration.

MRI/fMRI data collection and preprocessing

Resting-state fMRI data were acquired during 8 min of rest using echo planar imaging (EPI): [echo time (TE) = 30 ms; repetition time (TR) = 2000 ms; field of view (FOV) = 22 cm; flip angle = 80°; slice thickness = 4 mm, matrix = 64 × 64, in-plane resolution = 3.438 mm^2]. For localization of functional data, structural MRI was acquired using a high-resolution magnetization prepared gradient echo sequence (MPRAGE; TE = 4.38 ms; TR = 2000 ms, FOV = 220 mm; flip angle = 8°; slice thickness = 1 mm, NEX = 1, matrix = 256 × 256, in-plane resolution = 0.859 mm^2). Preprocessing of imaging data for each individual participant was carried out in AFNI (http://afni.minh.nih.gov.ezproxy.cul.columbia.edu). The following steps were completed in preprocessing after discarding the first five EPI volumes from each scan: slice time correction and three-dimensional motion correction with Fourier interpolation, time series despiking, and spatial smoothing (8 mm Gaussian kernel). Mean-based intensity normalization by the same factor was applied to all volumes. Data were temporally band-pass filtered with high pass (0.004 Hz) and low pass (0.1 Hz) filters. Data were then linearly and quadratically detrended. A deconvolution of the data was conducted to extract nine nuisance variables (white matter, cerebrospinal fluid, global signal, and six motion parameters). Linear registration of each participant's functional time series to the high-resolution MPRAGE was performed, and data were resampled to a 2 × 2 × 2 mm T1-weighted MNI standard template.

Memory Function

Tests of verbal memory (Hopkins Verbal Learning Test-Revised) and visuospatial memory (Brief Visuospatial Memory Test-Revised) were administered, and four scores were used for our primary analysis: HVLT-R Total Learning, HVLT-R Delayed Recall, BVMT-R Total Learning, BVMT-R Delayed Recall. Scores were converted to *t* scores using age-corrected norms. Participants were grouped according to memory status, with memory impairment defined as $T \leq 40$ on at least two of four memory tests, resulting in groups of memory-impaired ($n = 20$) and memory-intact ($n = 23$). A mean *t* score across the 4 measures was calculated for each group: memory-intact mean *t* score = 54.47, memory-impaired mean *t* score = 36.15; $p < .001$. The groups did not differ in disease duration (years; memory-impaired = 9.0 ± 2.9, memory-intact = 11.8 ± 7.4; $p = .131$), age (memory-impaired = 43.1 ± 8.8, memory-intact = 48.4 ± 9.4; $p = .063$), education (memory-impaired = 15.4 ± 2.3, memory-intact = 15.8 ± 2.1; $p = .48$), sex (memory-impaired = 2 M, memory-intact = 4 M; $p = .87$), disease subtype (memory-impaired: RR = 15, SP = 3, PP = 2; memory-intact: RR = 18, SP = 3, PP = 2), or physical disability (Ambulation Index: memory-impaired = 9.0 ± 4.6, memory-intact = 8.3 ± 2.1; $p = .51$).

Neuropsychological Battery

In addition to measurement of memory, a comprehensive battery of neuropsychological measures was administered,

Table 1. Results for each group from a comprehensive battery of neuropsychological measures administered

	Memory-intact	Memory-impaired	*p*	Cohen's *d*
Digit Span (total raw)	28.6 ± 5.9	27.2 ± 5.2	.43	—
COWAT (total raw)	47.5 ± 11.5	38.0 ± 12.0	.01*	0.81
PASAT (total raw)	48.6 ± 9.7	40.4 ± 13.7	.03*	0.69
SDMT (total raw)	54.5 ± 11.6	48.6 ± 12.8	.12	—
JoLO (total raw)	13.3 ± 2.1	12.0 ± 2.3	.05*	0.59
WTAR (SS)	111.0 ± 13.5	107.3 ± 12.2	.36	—
9HPT (mean L + R)	24.7 ± 4.8	28.2 ± 7.2	.07	—
Stroop Interference (total raw)	42.7 ± 10.8	39.5 ± 15.5	.42	—

COWAT = Controlled Oral Word Association Test, phonemic categories (FAS); PASAT = Paced Auditory Serial Addition Test, 3-s; SDMT = Symbol Digit Modality Test; JoLO = Judgement of Line Orientation; WTAR = Wechsler Test of Adult Reading; 9HPT = 9 Hole Peg Test.

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comprising tests of executive function, processing speed, visuospatial functions, language, and motor functions. Results of this battery for each group are presented in Table 1.

Statistical Analyses

FC was derived through seed-based analysis: correlations were computed for a 6-mm radius seed in PCC (x = 0, y = −50, z = 38) and each brain voxel. Thus, *Z*-corrected correlation (r) maps were generated for each subject. Maps were inspected on the individual level using InstaCorr in AFNI to verify that the default network was represented within each subject. On the group level, we ran one-way *t* tests to inspect r-maps for each group, that is, the integrity of the default network. Then, a *t* test was run using 3dttest in AFNI to compare r-maps between memory-impaired and memory-intact groups. To correct for multiple comparisons, an individual voxel probability was set at $p = .01$, with cluster threshold of >235 contiguous voxels significant at $p = .05$ (appropriate threshold using a Monte Carlo simulation as determined by AlphaSim). We expected MS patients with intact memory to show higher DN FC compared to MS patients with memory impairment. Average time series were extracted from four regions that withstood cluster thresholding. For each subject, correlations were calculated between FC for each region and four memory scores. We expected positive correlations, with higher FC associated with better memory performance. Using 3dRegAna, we reran the correlation controlling for atrophy [estimated by third ventricle width (TVW), as described in Benedict, Bruce, et al., 2006].

Specificity Analysis

Memory and cognitive efficiency are the most pervasive deficits seen in MS. As such, the additional tests of specificity were run to ensure that our results reflected memory status specifically, as opposed to cognitive status more generally. Thus, specificity of DN FC to memory (*vs.* disease-related cognitive decline more generally) was examined two ways. First, we re-ran our primary analysis controlling for

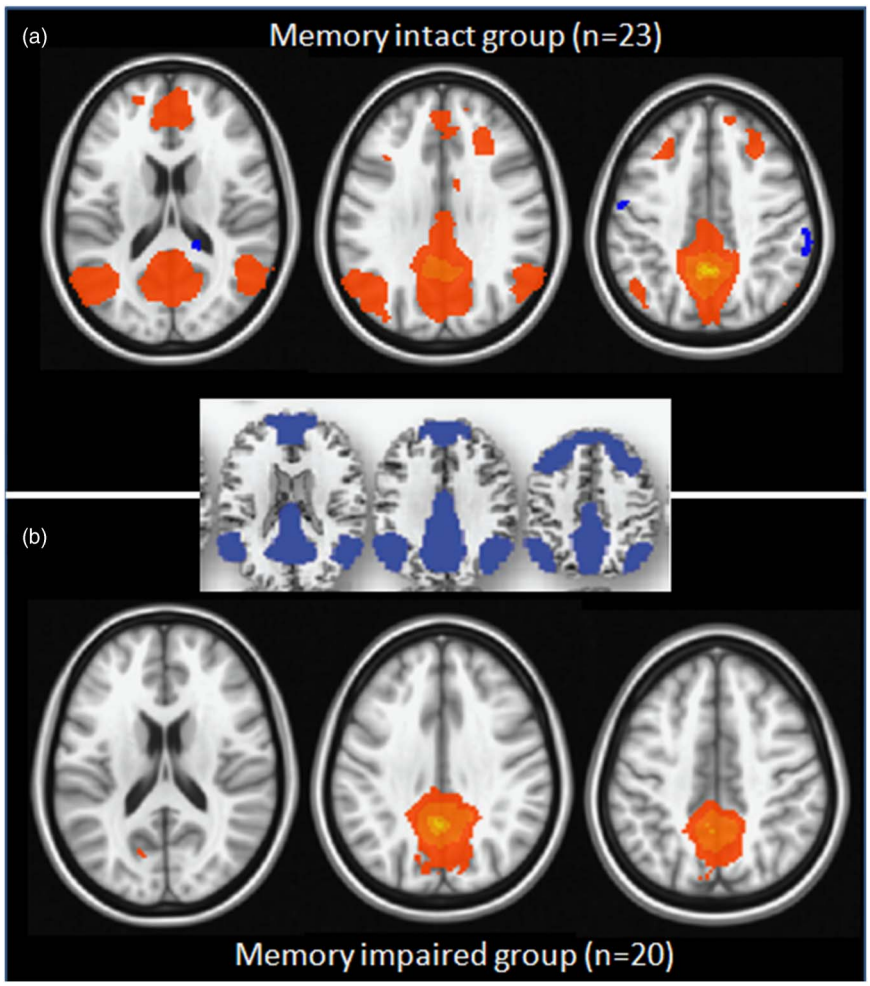

Fig. 1. a: PCC functional connectivity map for memory-intact group. For reference, middle panel shows the default network derived from 979 healthy adults (from Tomasi & Volkow, 2011). b: PCC FC map for memory-impaired group. (Individual voxel probability of $p = .001$. Cluster threshold = 28 consecutive voxels significant at $p = .001$ yields a corrected alpha of $p = .01$).

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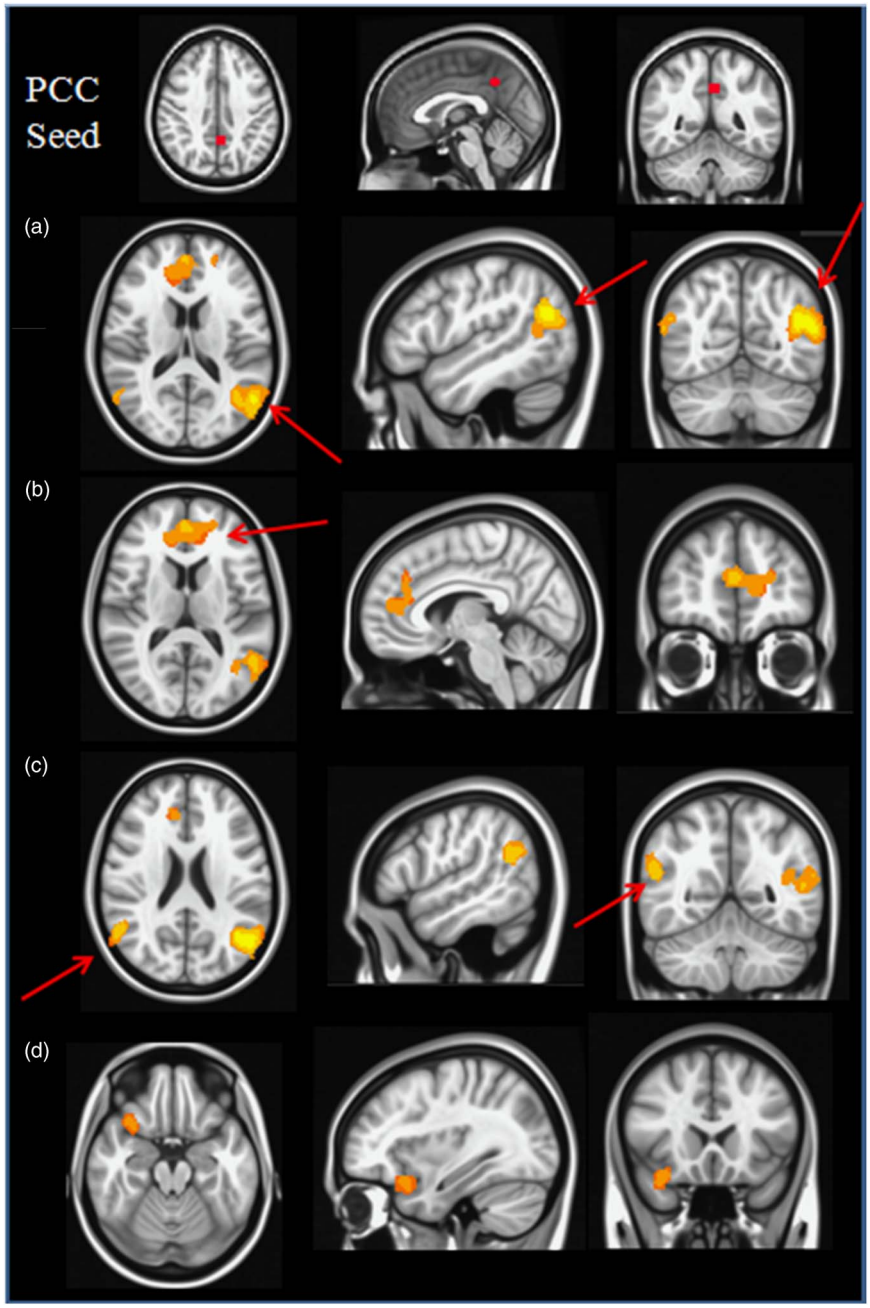

Fig. 2. Results of ttest ($p = .01$) comparing FC for memory-intact to memory-impaired patients with MS. For all regions (A-D), higher FC (orange) was seen in the memory-intact group compared to the memory-impaired group. The red dot is the seed ROI in PCC (x = 0, y = −50, z = 38; 6 mm radius). (All figures displayed are radiological convention, left = right, right = left).

cognitive efficiency [assessed with the Symbol Digit Modality Test (Benedict, Cookfair, et al., 2006)]. Using 3dRegAna, we examined the correlation of DN FC to memory status with cognitive efficiency (SDMT score) entered as a covariate. Next, we divided the group on the basis of cognitive efficiency, using a median split of SDMT scores to create cognitive efficiency-impaired and cognitive efficiency-intact groups. A correlation was then run to examine the association of DN FC to cognitive efficiency controlling for memory, thereby providing a direct analogue to our primary analysis.

RESULTS

An evaluation of default network functional connectivity in the memory-intact group revealed a map of functional integrity of the connections comprising the default network (see Figure 1a). In contrast, FC among DN hubs was not shown by the memory-impaired group (see Figure 1b).

A comparison of FC between groups of MS patients with and without memory impairment revealed four significant clusters ($p = .01$) where higher FC was shown by the memory-intact group compared to the memory-

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impaired group. These regions comprised left middle temporal gyrus, right anterior cingulate, right superior temporal gyrus, and right inferior frontal gyrus (Table 1; Figure 2). There were no regions where FC was lower for the memory-intact group compared to the memory-impaired group. The four regions that distinguished memory-impaired from memory-intact groups are primary DN hubs, supporting a key role of DN for memory function in MS. Furthermore, FC for all regions was positively correlated with memory performance on all memory measures, such that higher FC was consistently associated with better memory performance (Table 2). Our results did not change after controlling for atrophy.

To assess specificity of DN FC to memory function, we conducted two analyses. First, we re-ran the correlation of DN FC for the memory-intact and memory-impaired groups controlling for cognitive efficiency. Our results were largely maintained at $p = .01$, with stronger connectivity within the default network shown by the memory-intact group compared to the memory-impaired group (Figure 3), although two clusters fell out in this analysis, left middle temporal gyrus, and right inferior frontal gyrus.

Second, we divided our original group ($n = 43$) into two groups on the basis of cognitive efficiency status, yielding groups of cognitive efficiency-intact and cognitive efficiency-impaired. We examined DN FC differences between these groups, controlling for memory, and found no areas of significance. That is, there was no relationship between cognitive efficiency status and DN FC after controlling for the contribution of memory function. These findings bolster the case for specificity of DN to memory function, as opposed to signifying cognitive status more generally.

DISCUSSION

DN FC was higher in MS patients with intact memory compared to MS patients with memory impairment, highlighting a role of DN FC in the neurophysiologic basis of memory function in MS. These findings are consistent with results from memory-impaired populations such as Alzheimer's disease who show reduced DN FC (Greicius et al., 2004). Furthermore, specificity of DN FC to memory (*vs*. non-memory) function in MS was demonstrated herein, aligning our results with a prior report that used traditional task-based fMRI to support task-related DN activation as a sensitive and specific biomarker of memory function in MS (Sumowski, Wylie, Leavitt, Chiaravalloti, & DeLuca, 2012). The results of the present study augment that finding by providing evidence on the level of resting-state functional connectivity, which supports the role of the brain's intrinsic DN activity to strengthen memory function. Future longitudinal work to examine the association of DN FC to memory decline over time in MS may reveal DN FC as a predictive marker for memory decline.

An interesting finding regarding specificity was that of our four clusters comprising DN hubs, two fell away after

Table 2. Correlation of functional connectivity and memory performance collapsing over both groups

Cluster	Cluster size (# of voxels)	BA	Region	X	Y	Z	HVLT-TR	HVLT-DR	BVMT-TR	BVMT-DR
A	1334	39	Left middle temporal gyrus	−48	−64	24	r = 0.318, p = 0.038*	r = 0.486, p = .001**	r = 0.482, p = .001**	r = 0.443, p = .003**
B	1156	10	Right anterior cingulate	2	50	12	r = 0.305, p = 0.047*	r = 0.343, p = .024*	r = 0.538, p < .001**	r = 0.540, p < .001**
C	364	40	Right superior temporal gyrus	54	−54	22	r = 0.225, p = 0.148	r = 0.411, p = .006**	r = 0.495, p = .001**	r = 0.447, p = .003**
D	238	47	Right inferior frontal gyrus	34	20	−20	r = 0.550, p < 0.001**	r = 0.485, p = .001**	r = 0.439, p = .003**	r = 0.315, p = .039*

*$p \leq .05$, **$p \leq .01$. HVLT-R TR, DR = Hopkins Verbal Learning Test- Total Recall, Delayed Recall; BVMT-R TR, DR = Brief Visuospatial Memory Test- Total Recall, Delayed Recall.

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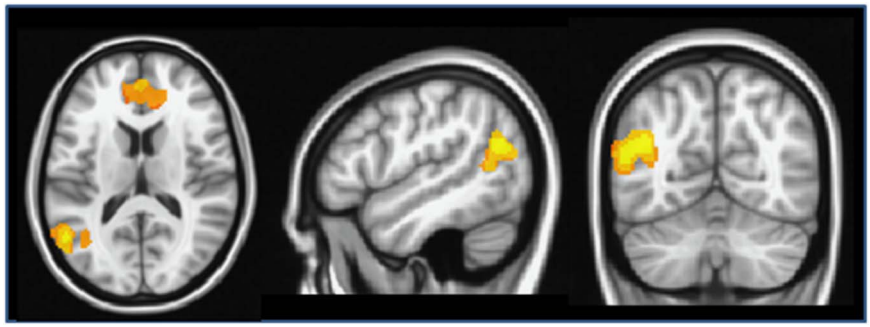

Fig. 3. Results of 3dANOVA ($p = .01$) comparing FC for memory-intact to memory-impaired patients with MS after controlling for cognitive efficiency.

controlling for cognitive efficiency. The two remaining clusters were robustly represented in this secondary analysis, and we can only speculate here as to why/whether these areas are more central to memory function. There is emerging evidence in the MS literature to suggest differences in connectivity within the network, (i.e., to anterior *vs*. posterior aspects of the network; Rocca et al., 2010), differences that may be related to compensatory changes due to disrupted white matter connections. These questions remain to be answered by future work inspecting the DN in greater depth to characterize its constituent parts. Longitudinal work could also address the possibility of FC changes across the disease course.

The findings presented herein reflect a novel approach to assessing DN FC in MS, as prior studies have not examined the specific link between DN FC and memory function (Hawellek et al., 2011; Rocca et al., 2010, 2012; Roosendaal et al., 2010). One recent MS study of FC within three different networks (including the DN) considered cognition on the basis of a single composite score combining memory with processing speed and working memory (Cruz-Gomez, Ventura-Campos, Belenguer, Avila, & Forn, 2014), a common approach in the MS cognition literature that unfortunately precludes interrogation of functional specificity of a network. Also unique to the present study was our comparison within a sample of MS patients (i.e., with *vs*. without memory impairment), rather than between MS patients and a healthy control group. Prior MS studies examining FC differences between healthy controls and MS patients have left open the possibility that disease-related variables may contribute to observed differences in DN FC between patients and controls, whereas here, we limited our investigation to MS patients with and without memory impairment, thereby isolating a single variable of interest. Finally, in contrast to prior studies, we used a seed-based approach for FC analysis, which allowed us to constrain our results to the PCC, the primary DN hub, (Greicius et al., 2003; Tomasi & Volkow, 2011), and investigate FC for this pre-selected region. An advantage of seed-based analysis is that it allows testing of constrained a priori hypotheses, and yields single metrics of connectivity for pairs of regions which can be useful for isolating network nodes of interest to test specific hypotheses relating FC to network function.

Limitations of the current study include a small sample size; future studies in larger MS samples should be done to strengthen these findings. Furthermore, to bolster the case for specificity of functional neuronal networks, a large-scale study of all of the brain's primary functional networks paired to their concomitant cognitive function should be conducted in persons with MS to determine whether our assertion of pairing behavior to neurophysiology will provide a clear direction for interpreting divergent evidence from the MS literature. The results reported herein were from cross-sectional data. Future work in longitudinal datasets should determine whether change in DN FC in MS patients is clinically meaningful, that is, related to memory function.

Identifying the neurophysiological basis for memory impairment in MS holds important implications for clinical care and treatment. Given the link between DN FC and memory function, the DN represents a novel candidate target for treatments to improve memory in MS. Moreover, FC may be a sensitive neural precursor and/or accompaniment to behavioral change. A recent preliminary report from our group showed aerobic exercise to improve memory in persons with MS, memory improvement that was supported by a neurostructural improvement (hippocampal volume increase), and a neurophysiological improvement (increased hippocampal FC) (Leavitt et al., 2014). Future treatment studies targeting cognitive and motor symptoms in MS may use functional connectivity within related networks as an outcome variable which may prove to be both sensitive and specific for a variety of functions.

Conversely, future research to elucidate risk factors for reduced DN FC should be pursued. Sleep is shown to be associated with increased DN FC (Killgore, Schwab, & Weiner, 2012); as such, sleep disorders frequently seen in MS constitute a risk factor for decreased DN FC, which may consequently impact memory function. Finally, as discussed, longitudinal work is needed to determine whether DN FC has predictive value for identifying MS patients at risk for memory decline. That is, although we know that approximately half of MS patients evince memory decline, we currently have no tools for identifying decliners. While patterns of altered FC have been previously observed across the entire brain of MS patients (both within and among

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large-scale networks), FC within the DN is shown to hold the strongest predictive value for discriminating between patients and healthy controls (Richiardi et al., 2012). The results of the present study support future investigations of DN FC for understanding and predicting memory decline in MS.

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