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Linking DMN connectivity to episodic memory capacity: What can we learn from patients with medial temporal lobe damage?

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ABSTRACT

Computational models predict that focal damage to the Default Mode Network (DMN) causes widespread decreases and increases of functional DMN connectivity. How such alterations impact functioning in a specific cognitive domain such as episodic memory remains relatively unexplored. Here, we show in patients with unilateral medial temporal lobe epilepsy (mTLE) that focal structural damage leads indeed to specific patterns of DMN functional connectivity alterations, specifically decreased connectivity between both medial temporal lobes (MTLs) and the posterior part of the DMN and increased intrahemispheric anterior–posterior connectivity. Importantly, these patterns were associated with better and worse episodic memory capacity, respectively. These distinct patterns, shown here for the first time, suggest that a close dialogue between both MTLs and the posterior components of the DMN is required to fully express the extensive repertoire of episodic memory abilities.

1. Introduction

A central tenet of the Human Brain Connectome project, which aims to accurately map the structural connectivity of the human brain, is that this structural architecture allows for rich functional network dynamics to unfold and these, in turn, enable an extensive repertoire of behaviours (Sporns, 2013; Sporns et al., 2005). Whereas many studies have begun to define the relationship between structural and functional connectivity (Honey et al., 2009; Evans, 2013), the link to cognition, especially on a network level, is still relatively unexplored. In the current study we address this major gap by examining how focal structural damage affects functional connectivity and how these disruptions map onto the specific cognitive deficit.

One of the striking findings of the research on brain connectivity is the establishment of the Default Mode Network (DMN), comprising the posterior cingulate, the medial prefrontal, and lateral parietal cortices, as well as the medial temporal lobes (MTLs), as a large-scale neurocognitive network and part of the core architecture of the brain (Hagmann et al., 2008; Raichle et al., 2001; Mesulam, 2012). Various neuroimaging techniques, including structural and functional magnetic resonance imaging (s/fMRI), have shown that nodes of the DMN are structurally and functionally highly interconnected with one another (Evans, 2013; Hagmann et al., 2008; Honey et al., 2010; Hosseini and Kesler, 2013). Further underscoring its centrality in the human brain, computational models predict that damage to DMN members causes widespread disruptions of functional connectivity within and beyond the DMN (Alstott et al., 2009). Specifically, these models predict that focal damage to the DMN causes decreased interhemispheric connectivity but increased intrahemispheric functional connectivity.

Of interest in the context of cognition, the DMN overlaps extensively with regions typically activated during autobiographical memory retrieval and has been suggested as a general recollection network (Spreng and Grady, 2010; Rugg and Vilberg, 2013). It is not surprising therefore that patients with widespread DMN damage, as for example in Alzheimer's disease, suffer from severely impaired episodic autobiographical memory function (Buckner et al., 2008). In contrast, patients with unilateral medial temporal lobe epilepsy (mTLE) suffer from a more focal DMN pathology, as epileptic seizures arise only from the medial temporal lobe (MTL). Moreover, patients with mTLE have a neuropsychologically selective impairment on episodic memory tasks,

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involving verbal memory (VM) with left mTLE and visuospatial memory (VSM) with right mTLE (Milner, 1972; Bell et al., 2011), and involving detailed autobiographical memory retrieval with either left or right-sided foci (St-Laurent et al., 2009, see for a review, McAndrews and Cohn, 2012). Therefore, these patients offer the opportunity to study the impact of focal structural DMN lesions on functional connectivity within the DMN and how these changes relate to a specific deficit in episodic memory.

There exist only a few studies that examine the relationship between unilateral MTL damage and functional connectivity within the DMN, and even fewer relating functional connectivity changes to specific neuropsychological profiles (Holmes et al., 2014; Holmes et al., 2013; McCormick et al., 2013a; Voets et al., 2009; Voets et al., 2012; Voets et al., 2014). For example, functional connectivity changes seen in mTLE (described below) can be attributed to changes in grey matter volume in constituent regions (Holmes et al., 2013; Voets et al., 2012). Further, linking functional connectivity to episodic memory capacity, we showed in an earlier study that stronger connectivity between the posterior cingulate cortex and the hippocampus (PCC–HC) on the epileptogenic side was associated with better material-specific memory capacity, and with greater postsurgical memory decline (McCormick et al., 2013a). In agreement with the idea that network integrity reflects cognitive capacity more accurately than focal integrity, the correlation between PCC–HC connectivity and episodic memory capacity was stronger than the relationship between hippocampal volume and episodic memory (i.e., focal structural integrity) and stronger than the relationship between hippocampal fMRI activation and episodic memory capacity (i.e., focal functional integrity as reported by Bonelli et al., 2010). Nonetheless, our previous study only focused on a single connection, PCC–HC, neglecting the overall functional status of the DMN. Whereas no study has yet related whole DMN integrity to episodic memory capacity to our knowledge, alterations of DMN connectivity and other functional networks underlying memory have been shown in mTLE (Zhang et al., 2010; Cataldi et al., 2013; Addis et al., 2007; Protzner and McAndrews, 2011; Pittau et al., 2012). Importantly, those networks are characterized by not only connectivity decreases but also increases (McCormick et al., 2013a; Addis et al., 2007; Bettus et al., 2010; Maccotta et al., 2013; Morgan et al., 2011) as predicted by virtual focal lesions to the DMN in computational models (Alstott et al., 2009). For example, whereas healthy controls rely on a hippocampal-centric effective network during autobiographical memory retrieval, patients with left mTLE bypass the affected hippocampus relying instead on increased intrahemispheric connectivity between posterior retrosplenial cingulate and anterior prefrontal cortices (Addis et al., 2007).

In this study, we addressed the following hypotheses: (1) focal structural damage to the MTL causes widespread DMN connectivity alterations; (2) those alterations follow a specific pattern that can be characterized by decreased interhemispheric connectivity and increased intrahemispheric connectivity; and (3) altered DMN patterns will reflect patient-specific episodic memory capacity.

2. Materials and methods

2.1. Participants

We included 101 participants in this study: 32 patients with right mTLE, 32 with left mTLE and 37 healthy participants. All participants gave written consent to this study which was approved by the UHN Research Ethics Board. Each patient had a diagnosis of unilateral mTLE based upon localization of seizure focus to the MTL during extended EEG and video monitoring. Presence of mesial temporal lobe sclerosis (MTS) was determined by a neuroradiologist at our epilepsy clinic (see Table 1 for demographic and clinical information).

Table 1
Clinical and demographical information.

	L-mTLE ($n = 32$)	R-mTLE ($n = 32$)	Controls ($n = 37$)	p-Value
General				
Sex, male/female	13/19	15/17	19/18	
Handedness, right/left/ambidextrous	28/3/1	28/4/0	33/4/0	
Age at scan, mean (SD)	36.5 (10.6)	37.7 (12.4)	35.1 (11.0)	0.65[a]
Education years, mean (SD)	15.2 (2.8)	13.5 (3.1)	15.9 (4.6)	0.03[a,d]
Clinical parameters				
MTS	22	20	–	
Other MRI lesions	3	8	–	
Age of onset, mean (SD)	19.9 (13.3)	19.2 (14.1)	–	0.83[b]
Behavioural data				
Verbal memory scores, mean (SD)	−0.51 (1.4)	0.20 (1.0)	–	0.01[c]
Visuospatial memory scores, mean (SD)	0.22 (0.9)	−0.60 (1.0)	–	0.03[c]
IQ scores, mean (SD)	0.26 (1.1)	0.12 (1.5)	–	0.68[b]

MTS = medial temporal lobe sclerosis; other MRI lesions for L-mTLE: 1 patient with left MTS and a small occipital cavernoma who received left selective amygdalohippocampectomy (at 1-year follow-up classified as seizure free, Engel 1), 1 patient with a single heterotopion in the occipital lobe who received standard anterior temporal lobe resection (at 1-year follow-up classified as seizure free, Engel 1), and 1 patient with left temporal pole dysembryoplastic neuroepithelial tumour (DNET) who did not yet receive surgery. This patient might have lateral TLE instead of medial TLE however visual inspection of the patients' data does not indicate an outlier. R-mTLE: 1 patient with right MTS and a small posterior temporal cavernoma, 6 with amygdala dysplasias (5 of these also had right hippocampal involvement), and 1 with right MTS and parahippocampal dysplasia.

[a] ANOVA.

[b] Two-sided t-test.

[c] One sided t-test.

[d] Post hoc t-test revealed that controls have more education years than patients with R-mTLE ($p < 0.05$).

2.2. Verbal and visuospatial memory components

For all patients, we calculated verbal memory (VM), visuospatial memory (VSM) and intelligence quotient (IQ) scores based on a previously described principal component analysis (PCA) from our lab (see detailed description in St-Laurent et al., 2014). In short, PCA was performed to reduce and summarize the number of measures obtained from extensive neuropsychological testing on 56 presurgical mTLE candidates (28 right mTLE and 28 left mTLE). Verbal memory measures included the Warrington Recognition Memory Test — Words (Warrington, 1984) and two measures from the Rey Auditory Verbal Learning Test (Strauss et al., 2006): a) the total number of recalled words over five trials and b) the percentage of words learned during the study phase that were recalled after a 20 min delay. Visuospatial memory measures included the Warrington Recognition Memory Test — Faces (Warrington, 1984), the total number of designs reproduced over five learning trials on the Rey Visual Design Learning Test (Spreen and Strauss, 1991) and the total number of trials to reach the learning criteria from the Spatial Conditional Associative Learning task (Petrides, 1985; Taylor et al., 1990). IQ measures included the Verbal and Performance IQ from the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999). PCA on the z-transformed test scores revealed three latent components that reflected a) verbal memory, b) visuospatial memory, and c) IQ. For the current study, individual test scores were z-transformed to the original 56 patients' distribution and PCA scores were calculated for each component by summing the product of each test's z-score and its corresponding coefficient. As expected, we found a material specific deficit in these patients, i.e., patients with left mTLE in comparison to patients with right mTLE had lower PCA scores on

the verbal memory component ($t = 2.4$, df $= 62$, $p = 0.01$) but higher PCA components on the visuospatial memory component ($t = 1.9$, df $= 62$, $p = 0.03$). In line with the view that the MTL is less pivotal for intelligence, the full scale Wechsler IQ of the patients fell well within the healthy range of the standard distribution (left mTLE, IQ $= 101.7 \pm 11.6$; right mTLE IQ $= 102.4 \pm 12.4$) and PCA scores of IQ did not differ between both patient groups ($t = 0.4$, df $= 62$, $p = 0.68$).

2.3. MRI acquisition

We acquired an anatomical MR image and 6 min of resting state fMRI for each participant. Participants were asked to let their mind wander and relax during scanning.

All MRI data were acquired on a 3 T Signa MR System (GE Medical Systems, Milwaukee, WI). The anatomical scans consist of a T1-weighted sequence, 146 slices, 220 mm FOV, 1 mm slice thickness, voxel size $0.86 \times 0.86 \times 1$ mm, 0 gap. T2*-weighted functional data were acquired in an interleaved order, between 28 and 32 slices to cover the whole brain, 240 mm FOV, 5 mm slice thickness, voxel size $3.75 \times 3.75 \times 5$ mm, 0 gap, TE $= 30$ ms, TR $= 2$ s. fMRI data were taken in an oblique orientation, with each slice being perpendicular to the long axis of the hippocampus. Patient and control MRI data were acquired between 2007 and 2013.

2.4. Regions of interest

As our hypotheses focused on the DMN, we chose 20 ROIs (8 mm spheres) based on coordinates specified in a recent comprehensive analysis of functional connectivity of the DMN (Andrews-Hanna et al., 2010) (see Table 2 for all ROIs and MNI coordinates). These DMN constituents have recently been corroborated by a study examining resting state fMRI connectivity in 1000 healthy subjects (Yeo et al., 2011). Important to the current study, Andrews-Hanna et al. (2010) showed in subsequent experiments that activity in these ROIs was associated with self-relevant, future-oriented and memory-directed behaviour. Therefore, we were confident that these regions are, when active, involved in episodic memory retrieval. Further, instead of using anatomically defined regions, we calculated grey matter volume (GMV) using the same 8 mm sphere ROIs. This approach allowed holding the voxel count constant among all DMN regions and between functional connectivity and structural analyses.

2.5. fMRI preprocessing and functional connectivity matrices of the DMN

All MRI data were preprocessed using the software package SPM8 (Statistical Parametric Mapping 8; http://www.fil.ion.ucl.ac.uk/spm/software/spm8). The first three frames of each fMRI session were dropped to allow signal equilibrium. Then, anatomical and functional images were reoriented to the anterior commissure and coregistered to the anatomical MNI T1 template. The anatomical images were segmented and normalized to the MNI T1 template. Functional data were realigned and unwarped and spatially normalized to the MNI T1 template using the normalization parameter created by the segmentation process. Further, fMRI data were smoothed with a full width half maximum (FWHM) of the Gaussian smoothing kernel of $8 \times 8 \times 8$ mm. The data were temporally bandpass filtered (0.01–0.1 Hz) and corrected for head motion (i.e., six head motion regressors from SPM realignment procedure), white matter and ventricular signal using the conn toolbox (http://www.nitrc.org/projects/conn).

To create functional connectivity (FC) matrices, time series of voxels within each of the 20 ROIs were averaged and correlated with the averaged time series of all other ROIs resulting in 190 correlation coefficients which were then transformed using Fisher's z calculation. Functional connectivity matrices were extracted using the conn toolbox.

Table 2
Regions of interest and MNI coordinates.

Region	Hemisphere	Abbreviation	x	y	z
Hippocampal formation	Left	lHC	−22	−20	−26
	Right	rHC	22	−20	−26
Parahippocampal cortex	Left	lPHC	−28	−40	−12
	Right	rPHC	28	−40	−12
Retrospenial cortex	Left	lRsp	−14	−52	8
	Right	rRsp	14	−52	8
Posterior inferior parietal lobule	Left	lIPL	−44	−74	32
	Right	rIPL	44	−74	32
Ventral medial prefrontal cortex	Midline	vmPFC	0	26	−18
Dorsal medial prefrontal cortex	Midline	dmPFC	0	52	26
Temporal pole	Left	lTempP	−50	14	−40
	Right	rTempP	50	14	−40
Lateral temporal cortex	Left	lLTC	−60	−24	−18
	Right	rLTC	60	−24	−18
Temporal parietal junction	Left	lTPJ	−54	−54	28
	Right	rTPJ	54	−54	28
Posterior cingulate cortex	Left	lPCC	−8	−56	26
	Right	rPCC	8	−56	26
Anterior medial prefrontal cortex	Left	lamPFC	−6	52	−2
	Right	ramPFC	6	52	−2
Anterior hippocampal ROI[a]	Left		−28	−12	−20
	Right		28	−12	−20
Posterior hippocampal ROI[a]	Left		−28	−38	−3
	Right		28	−38	−3

Coordinates are based on MNI system and represent the centre of 8 mm spheres. Left ROIs are built based on ROIs from Andrews-Hanna et al. (2010) Neuron.

[a] Additional ROIs to examine the relationship between GMV within the hippocampus and episodic memory capacity.

2.6. Voxel-based morphometry and GMV of the DMN

Voxel-based morphometry (VBM) analysis was performed using the default protocol for the VBM8 toolbox for SPM8 (http://dbm.neuro.uni-jena.de/vbm/). The T1 images were spatially normalized using the high-dimensional DARTEL normalization and segmented into grey matter, white matter and cerebrospinal fluid. Further, non-linear effects of the normalization were modulated so that GMV values describe the amount of grey matter relative to the voxel size. For example, if two grey matter voxels are squeezed into a single voxel, then the modulated value would be two because one normalized voxel would describe two grey matter voxels in native space. Further, sample homogeneity and segmentation results were examined to identify any outliers in the study sample but no images required exclusion. As a final step, modulated images were smoothed with an FWHM of the Gaussian smoothing kernel of $8 \times 8 \times 8$ mm.

We then extracted the averaged, relative GMV after correcting for different brain size from the same 20 ROIs as described above for each participant.

2.7. Statistical analyses

2.7.1. GMV and FC partial least squares analysis

We examined patterns of differences in FC and GMV between healthy controls and patients with mTLE, using partial least squares analyses. Detailed descriptions of PLS analysis can be found elsewhere (Krishnan et al., 2011; McIntosh et al., 1996). In brief, PLS uses singular value decomposition (SVD) to extract ranked latent variables (LVs) from the covariance matrix of brain data and experimental groups. For the current study, the brain data matrices for the FC-PLS contained 190 correlation coefficients (every possible connection between the 20 DMN ROIs) per subject and were grouped into healthy controls and patients with left and right mTLE. For the GMV-PLS, brain data matrices contained 20 GMV values from the 20 DMN ROIs per subject and were grouped again into healthy controls and patients with left and right

mTLE. The resulting LVs express patterns of brain data (e.g., strength of FC or amount of relative GMV) associated with each group. Statistical significance of the LVs was assessed using permutation testing. In this procedure, each subject's data was randomly reassigned (without replacement) to different experimental groups, and a null distribution was derived from multiple permuted solutions. In the current experiment, we used 500 permutations and considered LVs as significant if $p < 0.05$. Further, we assessed the reliability of each brain data entry that contributed to a specific LV's pattern using a bootstrap estimation of the standard error (i.e., bootstrap ratio, BSR). In this scenario, subjects were sampled randomly (100 times in total) with replacement and a new analysis was performed. In Table S1, we report BSRs greater than 2.00 for the FC-PLS and BSRs greater than 3.00 for the GMV-PLS. Additional information derived from PLS analyses are *brain scores* (i.e., similar to factor scores) for each individual that indicate the extent to which an individual expresses the pattern represented by the LV. This analysis results in a single map containing a BSR value for each ROI (GMV-EM-PLS). This BSR value then indicates whether GMV of that ROI differs significantly between healthy controls and a single patient group (e.g., patients with L-mTLE). This procedure was repeated for healthy controls and patients with R-mTLE and for the FC-PLS between groups. BSRs for individual ROIs or connections can be found in Table S1.

2.7.2. GMV-EM and FC-EM partial least squares

We examined whether functional connectivity or GMV of the DMN correlates with episodic memory measures in patients with mTLE, using a different version of PLS. This version examines the relationship between a behavioural measure, in our case episodic memory scores, and brain data as a function of the experimental group (Krishnan et al., 2011). The general difference to the previous PLS version is that, here, the covariance matrix used for SVD stems from correlation values between the behavioural measure (i.e., episodic memory capacity) and all other entries in the brain data matrix (i.e., rather than brain data matrices per group). For our GMV-VM/VSM and FC-VM/VSM-PLS, brain data matrices consisted again of either 20 GMV values or 190 FC values per patient, respectively. GMV and FC matrixes were correlated with behavioural measures, including verbal memory (VM), visuospatial memory (VSM) and IQ scores. To capture a greater variability of episodic memory performance, we concatenated across patients with left and right mTLE. Again, we used 500 permutations to assess significance of the LV and 100 bootstrap samples to assess reliable patterns. We considered functional connections (FC-EM-PLS) or ROIs (GMV-EM-PLS) with a BSR greater than 2.00 reliable. In contrast to the previous GMV- and FC-PLS, this analysis does not distinguish between two groups but results in a single map containing a BSR value for each ROI (GMV-EM-PLS). This BSR value then indicates whether GMV of that ROI correlates significantly with episodic memory capacity (e.g., verbal memory capacity). This procedure was repeated for visuospatial memory capacity and for the FC-EM-PLS correlations between DMN connectivity and episodic memory capacity. BSRs for individual ROIs or connections can be found in Table S1.

2.7.3. PCC–HC connectivity and episodic memory capacity

In a previous study, we found that stronger PCC–HC connectivity in the ipsilateral hemisphere was associated with better material-specific episodic memory capacity in patients with mTLE (McCormick et al., 2013a). In that study, we focused on the Warrington Words Recognition Test as a measure of verbal memory capacity in patients with L-mTLE and Warrington Faces Recognition Test as a measure of visuospatial memory capacity in patients with R-mTLE. In the current study, we aimed to examine whether these results would still hold true in the current, larger dataset and with our refined composite memory scores. A detailed description of the method used can be found elsewhere (McCormick et al., 2013a). In short, bilateral PCC-to-voxel connectivity maps for each individual were imported from conn into SPM8. For each patient group separately, a voxelwise one-sample *t*-test was conducted with one behavioural measure (e.g., verbal memory capacity) as a covariate of interest. An anatomical mask of both hippocampi were applied to the resulting images and thresholded at $p < 0.05$ small volume corrected (svc), cluster size > 10 voxels. This analysis indicates voxels within the hippocampi in which PCC–HC connectivity correlates with episodic memory capacity. Correlation values were then extracted from the peak hippocampal voxel for illustrative purposes.

2.7.4. Mediation analysis

To examine whether the influence of structural damage on episodic memory capacity is mediated by functional connectivity, we conducted a mediation analysis using the Aroian test (Aroian, 1944). In short, the Aroian test examines whether the unstandardized regression coefficient between the independent variable (i.e., structural integrity) and the dependent variable (i.e., episodic memory scores) decreases significantly if the mediator variable (i.e., functional connectivity) is included in the prediction model. Specifically, we conducted a series of simple and multiple linear regressions 1. between brain scores from the GMV-VM/VSM-PLS and episodic memory scores, 2. between brain scores from the FC-VM/VSM-PLS and episodic memory scores, 3. between brain scores from the GMV-VM/VSM-PLS and FC-VM/VSM-PLS analyses, and 4. between both GMV-VM/VSM-PLS and FC-VM/VSM-PLS brain scores and episodic memory. We then entered the unstandardized regression coefficients and standard errors of regression analysis 3 and 4 into the Aroian test. We considered a decrease of the regression coefficients of $p < 0.05$ significant. Of note, both GMV- and FC-VM/VSM-PLS maximize the correlation between GMV or FC and episodic memory and it is therefore not surprising that both GMV and FC predict episodic memory capacity significantly. However, we are not interested in this correlation per se (as it would be considered double-dipping, see Kriegeskorte et al., 2009) but in the mediating effect of functional connectivity. To test the specificity of the relationship between structural integrity, functional connectivity and episodic memory capacity, we also conducted a mediation analysis using functional connectivity as the independent variable and structural integrity as the mediator variable.

3. Results

3.1. Structural damage and functional connectivity alterations of the DMN in mTLE

As expected, patients with mTLE showed decreased grey matter volume of the ROIs situated in the affected medial temporal lobe, including the hippocampal formation and parahippocampal cortex in comparison to healthy controls (GMV-PLS, CTL and left mTLE, $p = 0.005$; CTL and right mTLE, $p = 0.002$, see Fig. 1A, Table S1 for BSRs and Fig. S1 for a general description of the DMN in controls and patients with mTLE). Additionally, patients with left mTLE also had decreased grey matter volume in the ROI situated in the left lateral temporal cortex and patients with right mTLE showed decreased grey matter volume in the ROI situated in the right temporal pole. There was no ROI that showed greater grey matter volume in patients than controls. Consistent with previous studies examining grey matter volume in mTLE (Keller and Roberts, 2008), these results indicate that mTLE is associated with grey matter volume loss primarily, though not exclusively, within the medial and lateral aspect of the affected temporal lobes.

In contrast to the marked grey matter volume decline concentrated in the affected MTL, we found widespread functional connectivity alterations within the DMN in patients with mTLE in comparison to healthy controls (FC-PLS, left mTLE $p < 0.001$; right mTLE $p < 0.009$, see Fig. 1B and Table S1 for BSRs). Interestingly, we found the same characteristic differences in both patient groups. First, in comparison to healthy controls, patients with mTLE showed reduced functional connectivity between the affected MTL and the posterior part of the DMN. That is, of the 23 connections that were significantly increased in controls relative to left mTLE patients, 11 involved ROIs of the MTL and the posterior part

of the DMN. A similar pattern was observed in the comparison of controls with right mTLE patients in that 6 of the 15 increased connections involved those ROIs. In contrast, very few such connections were increased in patients relative to controls (1 of 12 for left mTLE, 0 of 9 for right mTLE). Specifically, controls show strong interhemispheric connectivity between bilateral retrosplenial cortices and hippocampi, whereas patients with mTLE only had weak connectivity between these ROIs. Second, patients with mTLE showed a distinct pattern that was characterized by stronger intrahemispheric, anterior–posterior connectivity than healthy controls. Especially striking was the increased functional connectivity involving the ROIs situated in the prefrontal cortices. This was present in 7 out of 12 increased connections in left mTLE and only 2 of 23 increased connections for controls. A similar pattern was seen for right mTLE (5 of 9 connections) compared to controls (0 of 15 connections).

Further, linear regression analyses revealed that brain scores from the structural PLS strongly predicted brain scores of the functional connectivity PLS in both patient groups (see Fig. 1C, CTL and left mTLE, $r^2 = 0.24$, $p < 0.001$; CTL and right mTLE, $r^2 = 0.22$, $p < 0.001$). These findings are especially of interest because, as predicted by virtual lesions (Alstott et al., 2009), local structural DMN damage causes wide-spread functional connectivity alterations throughout this network. In fact, in both patient groups, these wide-spread disturbances of functional connectivity resulted in specific connectivity patterns (i.e., decreased posterior interhemispheric and increased anterior intrahemispheric connectivity).

3.2. Functional connectivity patterns related to individual differences in episodic memory capacity

We found that functional connectivity of the DMN indicated verbal (FC-VM-PLS, $p = 0.01$) and visuospatial memory capacity (FC-VSM-PLS, $p = 0.04$, see Fig. 2 and Table S1 for BSRs) in this patient cohort. Strikingly, the same functional connectivity patterns that separated healthy controls from patients before were now associated with better and worse episodic memory performance in the patient group. That is, connections associated with better verbal and visuospatial memory capacity mainly integrated the material-specific MTL into the posterior part of the DMN (VM: 5 of 7, VSM: 4 of 11 significant connections), whereas connections that were associated with impaired verbal and visuospatial memory capacity tended to be intrahemispheric connections and involve DMN nodes of the prefrontal cortex (VM: 11 of 18, VSM: 8 of 22 significant connections). Further, connectional involvement of the right temporal pole was also associated with worse episodic memory capacity (see Fig. 2 and Table S1 for BSRs). As the right temporal pole also showed decreased grey matter volume in patients with R-mTLE, a possible explanation for this involvement might be a higher spike and seizure propagation rate to the right temporal pole in patients with R-mTLE than in patients with L-mTLE. A recent study found that interictal epileptic spikes impair episodic memory function (Kleen et al., 2013) and it might therefore be that the involvement of the right temporal pole reported here might have been influenced by pathological brain activity. However, we found the same pattern separation in an additional analysis examining patterns associated with better and worse verbal memory capacity in patients with L-mTLE (L-mTLE, FC-VM-PLS, $p = 0.03$, see Table S2). For patients with R-mTLE, this additional analysis did not reach significance, nonetheless, the pattern separation was still visible (R-mTLE, FC-VSM-PLS, $p = 0.4$, see Table S2). Whereas the previous FC-PLS examined the central tendencies of differences between the groups' connectivity pattern, the current FC-VM/VSM-PLS examined individual differences and revealed that those patients who do better on clinical memory measures tend to rely on the pattern most associated with controls whereas those patients who do worse on memory testing tend to rely on the altered pattern that best characterizes the patient group as a whole. Therefore, these findings suggest that the greater the divergence of DMN connectivity from healthy controls, the worse episodic memory capacity in patients with mTLE. This finding is in line with a recent study showing that both decreased PCC–HC and increased hippocampal–entorhinal connectivity was associated with worse episodic memory capacity in patients with mTLE (Voets et al., 2014).

Finally, we examined whether DMN integrity indicates episodic memory capacity specifically and not other cognitive abilities, and we found that DMN connectivity did not reflect intelligence scores in mTLE patients (FC-IQ-PLS, $p = 0.91$).

As in our previous study, the connection between the PCC and the affected HC predicted better verbal and visuospatial memory capacity (McCormick et al., 2013a). Here, we extend this finding with a larger cohort of patients and refined composite memory scores rather than the single memory tests we used previously (see Fig. S2). Of note, patients in the earlier study are a subset of the current study cohort. Comparable to the previous findings, in patients with left mTLE, connectivity from the PCC to the left HC (PCC–lHC) correlated with verbal memory scores ($r^2 = 0.30$, $p = 0.001$) and in patients with right mTLE, connectivity from the PCC to the right HC (PCC–rHC) correlated with visuospatial memory scores ($r^2 = 0.18$, $p = 0.015$). However, brain scores reflecting the functional integrity of the entire DMN predicted verbal and visuospatial memory capacity more accurately than PCC–HC connectivity alone (see Fig. 3). In patients with left mTLE, DMN connectivity correlated with verbal memory scores ($r^2 = 0.61$, $p < 0.001$) and in patients with right mTLE, DMN connectivity correlated with visuospatial memory scores ($r^2 = 0.53$, $p < 0.001$). These results suggest that the overall integrity of the DMN is a more accurate marker for episodic memory capacity in mTLE than its individual connections.

In contrast to the strong relationships observed in the foregoing analyses, structural integrity of the DMN as a whole did not vary with verbal (GMV-VM-PLS, $p = 0.12$) or visuospatial memory capacity (GMV-VSM-PLS, $p = 0.41$) in patients with mTLE. Given the circumscribed seizure onset in mTLE, we further investigated the structural integrity of the hippocampus itself, using different hippocampal masks including total HC volume, ROIs situated in posterior and anterior HC segments (see Table 2 for MNI coordinates), and the ROI of the HC used in the current PLS analyses, to see if this could be a stronger associate of our memory scores. However, that was not the case (see Fig. S3). The majority of correlations were weak ($r^2 < 0.1$) and non-significant ($p > 0.1$), with only two regions demonstrating trends toward a relationship with verbal memory capacity (left HC, $r^2 = 0.05$, $p = 0.06$; left posterior HC $r^2 = 0.06$, $p = 0.06$).

3.3. Relationship of combined structural damage and functional connectivity alterations to predicting episodic memory capacity

As we noted earlier, our indicators of structural and functional integrity of the DMN are correlated, so we investigated whether any (albeit small) link between structural degradation and memory may be mediated by functional connectivity. A formal mediation analysis revealed this to be the case in that the unstandardized regression coefficient (i.e., B) between structural integrity (as measured by GMV-VM/VSM-PLS) and episodic memory (VM, B = 8.36; VSM, B = 3.28) dropped significantly when functional connectivity (as measured by FC-VM/VSM-PLC) was taken into account (VM, B = 3.06, Aroian test $p < 0.001$; VSM, B = 1.41, Aroian test $p = 0.029$). To highlight this directional influence, examining structural integrity as the mediator did not reveal significant results (VM, Aroian test $p = 0.07$; VSM, B = 1.41, Aroian test $p = 0.21$). Together, these findings support the idea that structural integrity shapes the possible dynamics of neuronal activity and that changing patterns of these dynamics underlie behavioural variability.

4. Discussion

In this study, we bring together a number of key observations that speak to the relationship between structural damage, functional

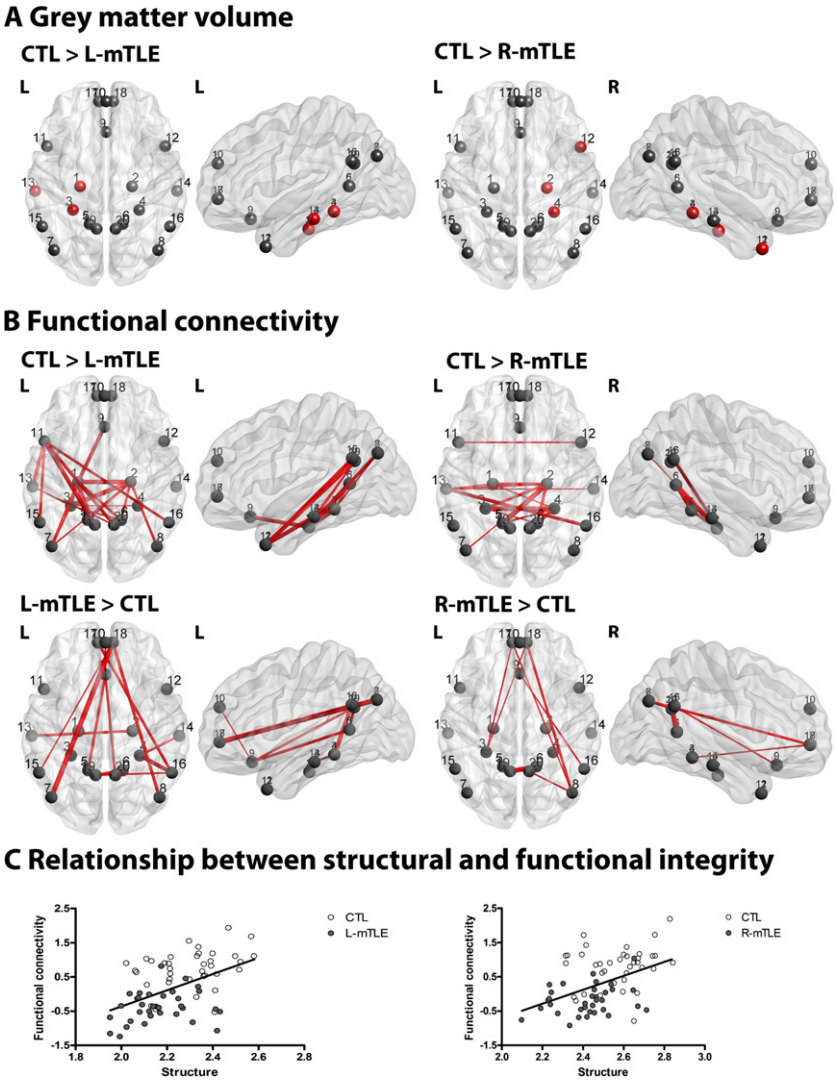

Fig. 1. DMN integrity. A. Red spheres illustrate ROIs in which patients with left (L- mTLE) and right mTLE (R-mTLE) have decreased grey matter volume (GMV) in com- parison to healthy controls (CTL). Of note, there were no increases of GMV in patients with mTLE in comparison to healthy controls. B. Red lines illustrate differences in func- tional connectivity between healthy controls than patients with left and right mTLE. The line thickness indicates the bootstrap ratio value. C. Correlation between brain scores resulting from the GM- and FC-DMN analyses in controls, R-mTLE and L-mTLE, indicating that the extent of structural DMN damage correlates with the extend of functional DMN connectivity alterations. See also Fig. S1 and Tables 2 and S1 . ROIs: 1. lHC and 2. rHC = left and right hippocampus, 3. lPHC and 4. rPHC = left and right parahippocampal cortex, 5. lRsp and 6. rRsp = left and right retrosplenial cortex, 7. llPL and 8. rlPL = left and right inferior parietal lobule, 9. vmPFC = ventromedial prefrontal cortex, 10. dmPFC = dorsomedial prefrontal cortex, 11. lTempP and 12. rTempP = left and right temporal pole, 13. lLTC and 14. rLTC = left and right lateral temporal cor- tex, 15. lTPJ and 16. rTPJ = left and right temporoparietal junction, 17. lamPFC and 18. ramPFC = left and right anterior medial prefrontal cortex, and 19. lPCC and 20. rPCC = left and right posterior cingulate cortex.

connectivity and cognitive capacity. First, we found wide-spread functional connectivity alterations throughout the DMN that correlated with the severity of structural damage confined largely to the ipsilateral medial and lateral temporal lobe. In line with our results, previous studies also found that functional connectivity alterations can at least be in part explained by structural damage (Holmes et al., 2013; Voets et al., 2012). Our findings converge with other recent studies indicating that the greater the structural damage to the MTL, the poorer the integration of this region with the DMN particularly in its posterior extent (Voets et al., 2012).

Second, we found distinct DMN connectivity patterns that separated patients with mTLE from healthy controls, in that controls showed greater posterior interhemispheric DMN and patients with mTLE greater anterior intrahemispheric DMN connectivity. Interestingly, virtual lesion models predicted these patterns in that damage to virtual DMN nodes results in widespread decreased interhemispheric and increased intrahemispheric connectivity (Alstott et al., 2009). Although not affecting the DMN directly, in line with this idea is a recent study showing that complete surgical separation of the two hemispheres in monkeys not only disrupted interhemispheric connectivity as expected but also increased intrahemispheric connectivity (O'Reilly et al., 2013). In mTLE, previous studies report mostly reduced functional connectivity to the damaged MTL, however, a growing number of studies also report increases of functional connectivity but these are inconsistent regarding the location and extent (McCormick et al., 2013a; Voets et al., 2014; Bettus et al., 2010; Maccotta et al., 2013; Morgan et al., 2011). One major difference between ours and previous studies is that they typically used single seed-based analysis whereas we used a multivariate pattern analysis that allowed us to examine altered patterns throughout but specific to DMN connectivity. That is, the specification of a single seed, for example, the damaged or contralateral medial temporal lobe, only examines a subset of DMN connections, i.e., from the medial temporal lobe to all other regions of the DMN. This approach might obscure effects of extra-MTL connections within the DMN, such as the pattern we identified in patients with mTLE. On the other hand, whole brain analysis (for example, independent component analysis, ICA) might obscure effects specific to the DMN (but see Voets et al., 2012 for an exception).

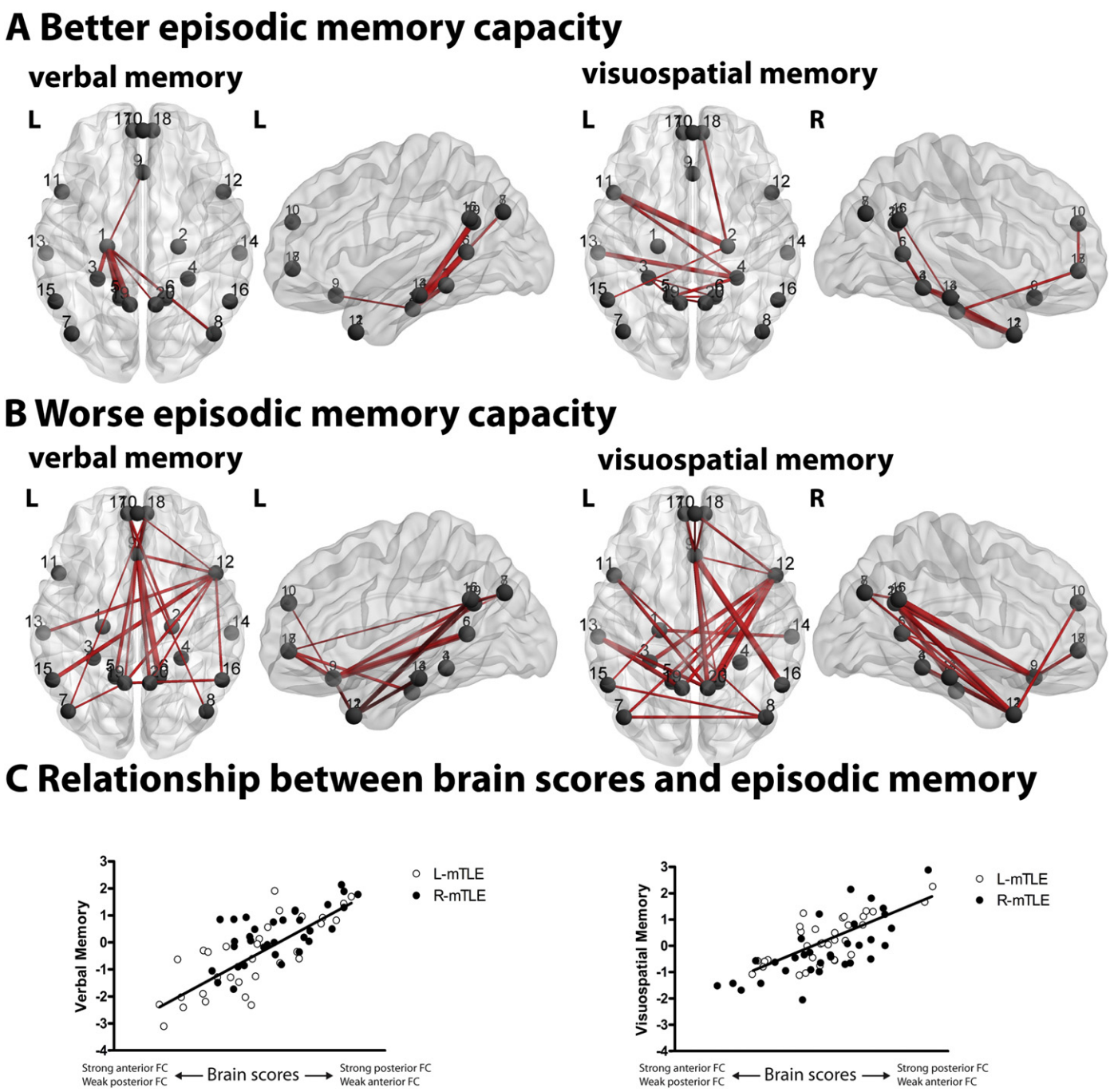

Fig. 2. Functional connectivity (FC) alterations of the DMN indicate episodic memory capacity in mTLE. Panel A illustrates networks that are associated with better episodic memory capacity and panel B illustrates networks that are associated with worse episodic memory capacity in patients with L-mTLE and R-mTLE. Significant connections are displayed in red. The line thickness indicates the bootstrap ratio value. See ROI description below Fig. 1 . Panel C displays the relation between brain scores (i.e., how well a participant expresses the above networks) and individual episodic memory capacity. For example, patients with higher brain scores have stronger connectivity within the network associated with better verbal memory and weaker connectivity within the pattern associated with worse verbal memory. FC = functional connectivity. See also Fig. S3 and Tables 2 and S1.

Third and in line with our previous observation (McCormick et al., 2013a), functional connectivity alterations of the DMN indicated episodic memory capacity reliably in patients with mTLE, but structural alterations did not. Whereas some studies indicate a relationship between structural integrity of the hippocampus and episodic memory (Poppenk and Moscovitch, 2011; Rausch, 1987), our results point to a more fundamental but indirect role of structural integrity. That is, the influence of structural DMN alteration on episodic memory capacity is mediated by alterations in functional networks. This finding is generally in line with the idea of the Human Brain Connectome project that the structural foundation of the brain enables its dynamic, functional repertoire which in turn is expressed as flexible behaviour (Sporns, 2013; Sporns et al., 2005; Honey et al., 2009; Honey et al., 2010).

Fourth, we show here for the first time that the whole pattern of functional DMN integrity captures between-subject variance in memory capacity better than focal activation or even one connection. This finding corroborates the idea that episodic memory capacity does not rely simply on the integrity of one region, even if that region, for example the hippocampus, is essential to episodic memory (McIntosh, 2000). Instead, our data indicate that episodic memory, even as measured in a

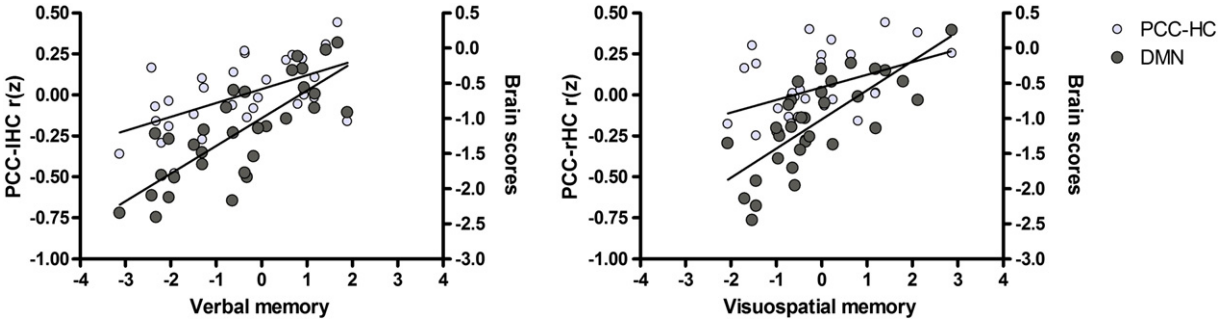

Fig. 3. Comparison between DMN and PCC–HC connectivity in predicting episodic memory capacity per patient group. Dots in light grey illustrate the correlation between episodic memory capacity and connectivity between the PCC and damaged HC (left y - axis) following the approach taken in McCormick et al. (2013a) . Dots in dark grey (same as in Fig. 2C) illustrate the correlation between episodic memory capacity and brain scores expressing the whole DMN integrity, as measured by the current approach (i.e., FC-VM / VSM-PLS, right y -axis). Of note, only patients with L-mTLTE contribute to the correlation with verbal memory (left graph) and only patients with R-mTLE contribute to the correlation with visuospatial memory (right graph). Verbal memory: PCC–lHC: $r^2 = 0.30$, brain scores: $r^2 = 0.61$; visuospatial memory: PCC–rHC: $r^2 = 0.18$, brain scores: $r^2 = 0.53$. DMN integrity is a better indicator of episodic memory than PCC–HC connectivity.

clinical setting that is expressly designed to assess memory capacity involving MTL regions, is supported by a large-scale brain network. Of course the DMN is not defined by a pattern of activation directly related to memory performance, but it is largely co-extensive with networks involved in memory retrieval such as the autobiographical memory network and recollection memory (Spreng and Grady, 2010; Rugg and Vilberg, 2013; Buckner, 2012). Nonetheless, the extent to which our findings can be generalized to memory networks defined by such tasks and beyond patients with mTLE, in whom longstanding seizures and structural damage may result in unique patterns of plasticity or remodelling, remains to be seen.

Lastly, we observed two distinct patterns of functional connectivity alterations that separated patients with mTLE from healthy controls on the one hand and that predicted better and worse episodic memory performance within this patient population on the other hand. These patterns might be best described as (1) a posterior interhemispheric network that integrates the MTL into the posterior part of the DMN and that was stronger in healthy controls and associated with better episodic memory capacity in patients and (2) an anterior intrahemispheric network that connects the prefrontal cortex with other parts of the DMN and that was stronger in patients with mTLE and associated with worse episodic memory capacity in them. While none of the current literature speaks to this distinction directly, a number of recent observations allows for some speculation. For example, recruitment of the posterior parts of the DMN and connectivity between them have been implicated in episodic memory retrieval, whereas recruitment of the anterior parts (i.e., prefrontal cortices) and connectivity between prefrontal and posterior cingulate cortices have been implicated in semantic memory retrieval (Shapira-Lichter et al., 2013). Further, we showed in an earlier study that the anterior hippocampus was strongly connected to a fronto-temporal network during the general search for an autobiographical memory, whereas bilateral posterior hippocampi were strongly connected to a widespread posterior network during the vivid, detail-rich elaboration of these autobiographical memories (McCormick et al., 2013b). Moreover in comparison to controls, patients with left mTLE show decreased connectivity of posterior medial regions to the left hippocampus during autobiographical memory retrieval but increased connectivity to the prefrontal cortex (Addis et al., 2007). Further strengthening the idea that the interhemispheric dialogue between the medial temporal lobes is crucial for vivid autobiographical memory elaboration, patients with either left or right MTL damage are able to retrieve the general gist of autobiographical memories but impaired at recovering specific details of those experiences (St-Laurent et al., 2009; St-Laurent et al., 2011). Thus, the distinct patterns of connectivity revealed in our data may reflect an important aspect of the fundamental organization of human memory, in that it is the dynamic interhemispheric communication between both medial temporal lobes and the posterior part of the DMN that is most crucial for vivid, detail-rich episodic retrieval of the kind that supports both recollection of autobiographical details as well as recall and recognition of material in clinical measures.

5. Conclusions

Our findings support the idea that focal structural damage leads to widespread functional connectivity changes within the DMN. By using multivariate analysis of functional connectivity matrices, we were able to extract functional networks within the DMN constituents that reflected differences between patients with MTL damage and healthy controls, and were further linked to episodic memory capacity. These patterns described here for the first time are especially interesting as they raise new questions about the neural organization of episodic memory.

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Appendix A. Supplementary material

Supplementary material associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.nicl.2014.05.008.

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