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Dissociated functional connectivity profiles for motor and attention deficits in acute right-hemisphere stroke

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Strokes often cause multiple behavioural deficits that are correlated at the population level. Here, we show that motor and attention deficits are selectively associated with abnormal patterns of resting state functional connectivity in the dorsal attention and motor networks. We measured attention and motor deficits in 44 right hemisphere-damaged patients with a first-time stroke at 1–2 weeks post-onset. The motor battery included tests that evaluated deficits in both upper and lower extremities. The attention battery assessed both spatial and non-spatial attention deficits. Summary measures for motor and attention deficits were identified through principal component analyses on the raw behavioural scores. Functional connectivity in structurally normal cortex was estimated based on the temporal correlation of blood oxygenation level-dependent signals measured at rest with functional magnetic resonance imaging. Any correlation between motor and attention deficits and between functional connectivity in the dorsal attention network and motor networks that might spuriously affect the relationship between each deficit and functional connectivity was statistically removed. We report a double dissociation between abnormal functional connectivity patterns and attention and motor deficits, respectively. Attention deficits were significantly more correlated with abnormal interhemispheric functional connectivity within the dorsal attention network than motor networks, while motor deficits were significantly more correlated with abnormal interhemispheric functional connectivity patterns within the motor networks than dorsal attention network. These findings indicate that functional connectivity patterns in structurally normal cortex following a stroke link abnormal physiology in brain networks to the corresponding behavioural deficits.

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Abbreviations: DAN = dorsal attention network; FC = functional connectivity; L/RHD = left/right hemisphere damage

Introduction

An important clinical and theoretical question is how damage to different parts of the brain, such as from a stroke, affects behaviour. This question has often been approached from a framework in which local structural damage to brain modules affects particular cognitive operations (Broca, 1863). However, since the seminal paper of von Monakov on diaschisis (von Monakow, 1911), several studies have shown that strokes also change the function of brain regions that are far from the site of local damage [Baron *et al.*, 1980; Perani *et al.*, 1987; Chollet *et al.*, 1991; Hillis *et al.*, 2002; Ward *et al.*, 2003; He *et al.*, 2007; Carter *et al.*, 2010; see also a recent review by Carrera and Tononi (2014)]. Critically, these distant physiological changes have been related to the behavioural deficits caused by a stroke (Hillis *et al.*, 2002; Ward *et al.*, 2003; He *et al.*, 2007; Carter *et al.*, 2010; Wang *et al.*, 2010; Park *et al.*, 2011; Baldassarre *et al.*, 2014).

An important advance of the last decade has been to link distant physiological changes in activity to the functional organization of brain networks. Measurements of the temporal correlation of blood oxygenation level-dependent (BOLD) signals between different brain regions in the absence of a task (Biswal *et al.*, 1995; Fox and Raichle, 2007) called resting state functional connectivity (FC), can be used to map network topography (Doucet *et al.*, 2011; Power *et al.*, 2011; Yeo *et al.*, 2011; Hacker *et al.*, 2013; Cole *et al.*, 2014; Gordon *et al.*, 2016). Accordingly, recent studies have measured resting state FC in order to determine the effects of stroke on brain networks and link abnormalities in those networks to behavioural deficits (Carter *et al.*, 2012*b*; Varsou *et al.*, 2013).

A primary goal has been to associate the dysfunction of particular brain networks identified in healthy subjects (Doucet *et al.*, 2011; Power *et al.*, 2011; Yeo *et al.*, 2011; Hacker *et al.*, 2013; Cole *et al.*, 2014; Gordon *et al.*, 2016) with particular kinds of behavioural deficits post-stroke. For example, resting dysfunction of the dorsal attention network (DAN), which includes regions in posterior parietal cortex, frontal eye fields, and MT+ (Corbetta and Shulman, 2002), has been related to unilateral spatial neglect (He *et al.*, 2007; Carter *et al.*, 2010). The strongest abnormality is a decrease in the magnitude of interhemispheric FC, not only within the DAN but also within auditory and motor networks (Baldassarre *et al.*, 2014). Similarly, several reports have shown that resting FC abnormalities in the motor network are correlated with motor deficits in humans (Carter *et al.*, 2010, 2012*a*; Wang *et al.*, 2010; Park *et al.*, 2011; Yin *et al.*, 2012; Chen and Schlaug, 2013) and rodents (van Meer *et al.*, 2012; Bauer *et al.*, 2014; Grefkes and Fink, 2014). Again the most common and robust disruption is a decrement of interhemispheric connectivity in the motor network. These studies support the idea that behavioural deficits post-stroke are not only related to the site of damage, but also to the physiological dysfunction of distributed brain networks.

However, the behavioural specificity of resting FC abnormalities in stroke populations is currently unclear, as almost every study has investigated FC–behaviour associations in either single behavioural domains, e.g. attention or motor; single networks, e.g. DAN; or motor networks, or both. No study has shown that after stroke, different patterns of abnormal FC are related to distinct patterns of behavioural dysfunction. In a prior study (Carter *et al.*, 2010) we examined the relationship in stroke patients between multiple behavioural deficits and abnormal FC in multiple networks. We reported that motor deficits were equally correlated with FC in motor and dorsal attention networks. Attention deficits showed a higher correlation for FC DAN than motor deficits, but the difference was not significant. Therefore, our results did not clearly support the behavioural specificity of FC after stroke.

A limitation of previous studies linking abnormal FC to motor or attention deficits is that correlations between those deficits were not taken into account. Such correlations might inflate the relationship between a particular behaviour and FC in a particular network, as well as the overall degree to which the behaviour is related to FC. For example, if patients with right hemisphere strokes tend to have both attention and motor deficits, then correlations between one type of behavioural deficit, e.g. motor, and resting FC in a network could actually reflect a relationship involving the other behavioural deficit, e.g. attention. In fact, strokes often produce correlated behavioural deficits (Corbetta *et al.*, 2015). A stroke that damages both the internal capsule and basal ganglia in the right hemisphere may produce unilateral spatial neglect, a general slowing of reaction time, spatial memory deficits, and motor dysfunction of the left side, the latter including impairments in strength, range of motion, and coordination (Corbetta *et al.*, 2015).

Similarly, correlations between the FC of the DAN and motor network could also inflate the relationship between a particular behaviour and FC in a particular network. For example, if FC in the DAN and motor network were highly correlated, a strong association between attention deficits and DAN FC would also result in an association between attention deficits and motor network FC. Therefore, to show the specificity of the relationship between a particular behaviour and FC in a particular network, both correlations between different behaviours and correlations between the FC of different networks need to be taken into account.

The primary goal of the current work was to determine whether motor and attention deficits are related to abnormal patterns of resting FC in the motor network and DAN, respectively. We studied a large heterogeneous sample of subacute (2 weeks post-onset) right hemisphere stroke patients, and used partial correlation techniques to identify the unique relationship between a given impairment, e.g. attention, and the interhemispheric FC of a given network, e.g. the DAN. In addition, because the DAN and motor network involve both segregated and overlapping regions of cortex at the whole brain level, we analysed the segregated parts of each network. Accordingly, the association of behavioural deficits with the interhemispheric FC between regions of interest in one hemisphere and voxels in the other hemisphere, was measured for voxels that were relatively uniquely associated either with the DAN or motor network. Finally, recent work in our laboratory indicates that FC measures are affected in ~20–30% of acute stroke patients at 1–2 weeks post-onset by haemodynamic lags that can influence the correlation between FC and behaviour (Siegel *et al.*, 2015). This important factor has not been controlled in previous studies. Hence all analyses in this study were controlled for the potential influence of lags.

Materials and methods

Participants

Stroke patients

All patients were recruited from the stroke service at Barnes-Jewish Hospital (BJH), with the help of the Washington University Cognitive Rehabilitation Research Group (CRRG). All participants provided informed consent approved from the Washington University Institutional Review Board (IRB). As described in Corbetta *et al.* (2015), subjects were not enrolled based on specific deficits, but prospectively based on the presence of any neurological deficit after a first time stroke. This sample is representative of the source population of stroke patients at BJH in Saint Louis (Corbetta *et al.*, 2015). Inclusion criteria were as follows: (i) clinical diagnosis of stroke (ischaemic or haemorrhagic) at hospital discharge; (ii) persistent stroke symptom(s) at hospital discharge; (iii) awake, alert, and able to complete study tasks; and (iv) age 18 or older. Exclusion criteria were as follows: (i) previous stroke; (ii) multifocal stroke; (iii) schizophrenia, bipolar disorder, major depression, or other severe psychiatric condition; (iv) dementia (as measured by a Short Blessed Score of $\geqslant 9$, or as measured by a premorbid AD-8 score of $\geqslant 2$); (v) epilepsy, Parkinson's disease, or other neurological disorder; (vi) brain injury; (vii) end stage renal disease, terminal cancer, class III or IV heart failure, or other diagnosis with a life expectancy <1 year; (viii) premorbid functional disability as measured by a modified Rankin score of $\geqslant 2$; (ix) claustrophobia; or (x) implanted metal precluding 3 T MRI.

An initial cohort of 85 patients [49 male, average age 52.8 years, standard deviation (SD) = 10.6 with a range from 19 to 72 years], which included 51.7% ($n = 44$) right hemisphere-damaged (RHD) patients and 48.3% ($n = 41$) left hemisphere damaged (LHD) patients, was recruited. However, because of the low frequency of LHD patients showing an attention deficit (see 'Results' section), the analysis was restricted to RHD patients, which included six patients with haemorrhagic stroke and 38 patients with ischaemic stroke. Moreover, one RHD patient with an ischaemic stroke was excluded from the FC-behaviour analyses because of the low number of BOLD frames that survived the scrubbing procedure for head motion. Thus, the final sample included in the FC–behaviour analyses consisted of 43 RHD patients (23 males) with an average age of 52.6 years (SD = 8.5; range between 37 and 70 years; see Table 1 for demographic data and NIH Stroke Scale scores at admission to the hospital).

Age-matched control subjects

A group of 30 healthy individuals without any neurological or severe psychiatric history (average age 55.7 years, SD = 11.5, with a range from 21 to 83 years), matched for age and education with the stroke sample, was also studied. This group of age-matched control subjects was only used for computing cut-off scores for categorizing patients as having motor and attention deficits. As explained below, the primary analyses examining the relationship between FC and behaviour were conducted strictly within the patient sample. Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

Young controls

An independent sample of 21 young healthy control subjects (seven male, average age 24.6 years, with a range from 23 to 35 years) was used, as described in our previous work (Hacker *et al.*, 2013), to define regions of interest and to generate voxel-wise templates of the DAN and motor network.

Behavioural testing

Two authors (J.S. and K.Z., patient coordinators for the study) conducted the neuropsychological assessment on average 13 days following the stroke (SD = 4.3). The MRI scans were conducted within 24 h of the assessment. Behavioural testing was carried out in a quiet exam room. The tests described here are a subset of a comprehensive battery of motor, attention, vision, language, and memory function recently described in Corbetta *et al.* (2015).

Assessment of attention

We used the Posner visual orienting task (Posner, 1980; Posner *et al.*, 1984; Kincade *et al.*, 2005) and two cancellation tests, the Mesulam Unstructured Symbol Cancellation Test (Mesulam, 1985), and the Behavioural Inattention Test (Wilson *et al.*, 1987). These tests were selected for their high sensitivity both at the acute and chronic stage (Rengachary *et al.*, 2011), and were the same as in our previously published work on neglect (Baldassarre *et al.*, 2014).

Computerized Posner cueing task

Stimuli were generated by an Apple Power Macintosh computer and displayed on a 17-inch Apple Monitor. Responses were recorded through a Carnegie Mellon button box interfaced with the computer. The experimenter monitored eye movements and encouraged visual fixation whenever a fixation

Table 1 Demographic and clinical characteristics of the RHD patients (n = 43)

ID	Age at stroke	Gender	Days since stroke	tPA	Type of lesion	Lesion volume (mm^3)	Lesion site	Acute NIHSS (range:0–42; 0 = normal)
1	49	M	12	N	I	3176	S	5
2	70	F	18	N	I	3120	S	8
3	66	M	14	N	I	47 976	C-S	13
4	47	M	8	N	I	34 200	S	6
5	54	F	10	N	I	3360	B	11
6	63	F	7	N	I	21 032	S	11
7	56	F	12	N	I	832	S	4
8	52	M	10	N	I	11 192	C-WM	3
9	53	M	10	N	I	2352	S	4
10	50	M	8	N	I	952	B	6
11	60	M	9	N	I	5896	S	8
12	64	F	12	N	I	104	B	5
13	63	F	16	N	I	81 488	C-S	10
14	43	F	11	N	I	18 200	C	1
15	47	M	13	N	I	1168	C	2
16	37	M	7	N	I	10 656	CBL	0
17	57	M	8	N	I	888	S	5
18	61	F	12	Y	I	47 248	C-S	2
19	51	F	14	N	I	2584	C	1
20	57	M	9	N	I	20 520	C-S	2
21	52	M	12	Y	I	728	B	5
22	58	M	23	N	H	1864	B	7
23	59	M	12	N	H	21 096	S	1
24	56	M	16	N	I	13 744	WM	12
25	54	F	14	N	I	2504	C-S	2
26	50	F	16	N	I	1896	S	1
27	44	M	15	N	H	24 616	S	0
28	62	M	12	Y	I	75 800	C-WM	10
29	40	F	11	Y	I	22 256	S	1
30	40	F	19	N	I	82 400	C-S	12
31	62	F	12	Y	I	7992	S	16
32	40	M	27	N	I	1536	S	0
33	39	F	21	N	I	1608	S	5
34	57	M	8	N	I	5856	CBL	2
35	51	M	11	Y	I	67 176	C-S	25
36	47	F	13	N	I	29 200	C-S	1
37	39	M	10	N	I	50 520	C-S	9
38	50	M	14	N	I	5288	CBL	2
39	39	F	15	Y	I	37 952	C-S	11
40	52	F	11	N	H	21 688	S	6
41	51	M	13	N	I	4304	CBL	0
42	52	F	17	N	H	14 432	B	12
43	70	F	19	N	H	5280	C-S	0
Total		23 M/20 F		7 Y/36 N	37 I/6 H			
Mean	52.65		13.05			23 050		5.74
SD	8.58		4.25			18 992		5.31

B = brainstem; C = cortical; CBL = cerebellum; C-S = cortico-subcortical; C-WM = cortical-white matter; H = haemorrhagic; I = ischaemic; N = no; NIHSS = National Institutes of Health stroke scale; S = subcortical; tPA = tissue plasminogen activator treatment; WM = white matter; Y = yes.

break occurred. The display contained a central fixation cross and two eccentric, square frames (side 1°, centre of frame at 3.3° from the fixation cross) positioned to the left and right of fixation along the horizontal meridian. The onset of a new trial was signalled by a colour change of the fixation cross from red to green, 800 ms later an arrow cue pointing left or right appeared at fixation for 2360 ms. Following a delay ranging from 1000 to 2000 ms, the target (an asterisk) appeared for 300 ms within the left or right frame. On 75% of the trials, the target appeared at the location indicated by the cue (valid condition); on 25% of the trials it appeared at the opposite location (invalid condition). Participants had to detect the

target as quickly as possible with a key press. Patients responded using the unaffected hand; control subjects responded using the dominant hand. Reaction times and errors, consisting of no response or a reaction time >2000 ms, were recorded. An intertrial interval of 2360 ms separated subsequent trials. Blocks contained 30 valid and 10 invalid trials. Each patient completed two blocks. The Posner cueing test took a total of 15 min to administer including a practice block.

Mesulam Unstructured Symbol Cancellation Test

The Mesulam cancellation test (Mesulam, 1985), consists of a pseudo-random array of 60 target symbols with several hundred distracters, presented on paper. We calculated the centre of cancellation, i.e. the lateralized centre-of-mass of hits, using the software provided by Rorden and Karnath (2010), for contralesional versus ipsilesional hits.

Behavioural Inattention Test: Star cancellation subtest

The Behavioural Inattention Test (Wilson *et al.*, 1987) consists of a pseudo-random array of 54 targets with 52 distracters, presented on paper. Subjects responded with pencil marks. We calculated the centre of cancellation, i.e. the lateralized centre-of-mass of hits, using the software provided by Rorden and Karnath (2010), for contralesional versus ipsilesional hits.

Assessment of motor function

Motor deficits were assessed using a battery that tested both upper and lower extremity impairment and function. The tests included in the battery were selected based on the findings of previous studies that investigated limb functionality in stroke (Ward *et al.*, 2003; Lang *et al.*, 2005, 2006). Upper body tests included: active range of motion against gravity, measured by goniometry at shoulder flexion, and wrist extension (Dreeben-Irimia, 2008); grip strength, measured by dynamometry (Schmidt and Toews, 1970; Demeurisse *et al.*, 1980); dexterity, measured with the 9-Hole Peg Test, in which patients placed nine plastic pegs into holes on a pegboard as quickly as possible (pegs/s; Mathiowetz *et al.*, 1985); and function, measured with the Action Research Arm Test total score (ARAT). Patients performed functional grasp, grip, pinch, and gross motor movements that were rated for the quality of the movement according to a standardized protocol (Oxford Grice *et al.*, 2003).

Lower body tests included the combined walking index, left/right total motricity index, and ankle dorsiflexion goniometry.

For the combined walking index, patients were timed while walking 10 m if able to safely do so unassisted. Patients who were unable to walk 10 m were rated using the Walking item on the Functional Independence Measure. The following variable was recorded as a combined index of the two walking measures to capture variability both for maximally and minimally impaired patients: score of 1 = total assistance required to walk; score of 2 = maximal assistance required to walk; score of 3 = moderate assistance required to walk; score of 4 = minimal contact assistance required to walk; score of 5 = standby assistance required to walk; score of 6 = modified independence in walking (use of assistive device); score of 7 = independence in walking but a speed of <0.4 m/s; score of 8 = independence in walking but a speed of 0.4 to 0.8 m/s; score of 9 = independence in walking and a speed >0.8 m/s. Note that 0.4–0.8 m/s denotes household ambulation, whereas >0.8 m/s denotes community ambulation (Keith *et al.*, 1987; Perry *et al.*, 1995; Kempen *et al.*, 2011).

The left/right total motricity index sums the manual muscle testing scores for left/right hip flexion, knee extension, and ankle dorsiflexion; and ankle dorsiflexion goniometry for left/right active range of motion against gravity (Dreeben-Irimia, 2008).

Analysis of behavioural scores

The scores of the attention battery conducted on all patients (n = 85) were analysed with the same procedure described previously (Baldassarre *et al.*, 2014). Specifically, six measures were derived from the Posner task scores: Posner Overall Attention (mean performance), Posner Visual Field Bias (difference in performance for targets presented in the ipsilesional versus contralesional visual field) and Posner Validity Effect (difference in performance for validly versus invalidly cued targets), with separate measures for reaction time and accuracy. For the Mesulam and Behavioural Inattention Test tests, we calculated the Centre of Cancellation, that is, the lateralized centre of mass of hits, using the software provided by Rorden and Karnath (2010), for contralesional versus ipsilesional hits. For each patient, the six measures from the Posner task and the Centre of Cancellation (Rorden and Karnath, 2010) scores from the Mesulam and Behavioural Inattention tests were entered into a factor analysis with oblimin rotation performed using Statistical Package for the Social Sciences (SPSS, v.20) software. A similar factor analysis was performed on eight scores from the motor battery: shoulder flexion, wrist extension, grip strength, pegboard performance, ARA total score, motricity index, ankle dorsiflexion, and combined walking index.

Functional MRI

Scanning

MRI scanning was performed with a Siemens 3 T Tim-Trio scanner at the Washington University School of Medicine (WUSM) by A.B., L.R., and N.M. Imaging data were collected for research purposes only. Structural scans consisted of: (i) a sagittal T_1-weighted MP-RAGE (repetition time = 1950 ms, echo time = 226 ms, flip angle = 9°, voxel size = 1.0 × 1.0 × 1.0 mm); (ii) a transverse T_2-weighted turbo spin-echo (repetition time = 2500 ms, echo time = 442 ms, voxel size = 1.0 × 1.0 × 1.0 mm); and (iii) sagittal FLAIR (fluid attenuated inversion recovery; repetition time = 7500 ms, echo time = 326 ms, voxel size = 1.5 × 1.5 × 1.5 mm). Resting state functional scans were acquired with a gradient echo EPI sequence with repetition time = 2000 ms, echo time = 27 ms, 32 contiguous 4 mm slices, 4 × 4 in-plane resolution, during which participants were instructed to fixate on a small white cross displayed on a black background in a low luminance environment. Seven resting state functional MRI runs, each including 128 volumes, were acquired. Each run lasted 4.26 min. Between runs there was a 30–60-s period during which subjects were reminded that during a run they should maintain their eyes fixated on the cross, stay awake, and not move.

Data preprocessing

Functional MRI data underwent preprocessing as previously described (Shulman *et al.*, 2010), which included the following steps: (i) compensation for asynchronous slice acquisition using sinc interpolation; (ii) elimination of odd/even slice intensity

differences resulting from interleaved acquisition; (iii) whole brain intensity normalization to achieve a mode value of 1000; (iv) spatial realignment within and across functional MRI runs; (v) resampling to 3 mm^3 voxels in atlas space including realignment and atlas transformation in one resampling step. Cross-modal, e.g. T_2-weighted $\rightarrow$ T_1-weighted, image registration was accomplished by aligning image gradients (Rowland *et al.*, 2005). Cross-modal image registration in patients was checked by comparing the optimized voxel similarity measure to the 97.5th percentile obtained in the control group. In some cases, structural images were substituted across sessions to improve the quality of registration.

In preparation for the FC MRI analysis, data were passed through several additional preprocessing steps (Fox *et al.*, 2005, 2009): (i) spatial smoothing consisting of 6 mm full-width at half-maximum Gaussian blur in each direction; (ii) temporal filtering retaining frequencies band below 0.1 Hz; (iii) removal of the following sources of spurious variance unlikely to reflect spatially specific functional correlations through linear regression: (a) six parameters obtained by rigid body correction of head motion; (b) the whole-brain signal averaged over a fixed region in atlas space; (c) signal from a ventricular region of interest; and (d) signal from a region centred in the white matter.

Quality control of resting-state functional MRI data

Prior to the functional connectivity mapping, motion contaminated frames were identified using the DVARS measure (root mean squared change of the temporally differentiated functional MRI data averaged over the brain; Power *et al.*, 2012). The DVARS criterion for high motion frames was defined as 2 SD above the mean DVARS in the age- and education-matched control subjects, corresponding to 0.46 RMS functional MRI signal change in units of %. This frame-censoring criterion was uniformly applied to all resting state functional MRI data including patients and controls, prior to functional connectivity computations. Motion-contaminated frames were not included in the computation of resting state FC.

Previous studies have reported that the haemodynamic response can show substantial delays following a stroke (Pineiro *et al.*, 2002; Salinet *et al.*, 2013). As these delays can affect FC measurements, we calculated the lag scores in each patient as follows. For each subject, the mean grey matter signal was extracted by averaging over the grey matter mask segmented by FreeSurfer 5.3 (Fischl, 2012), excluding any voxels within the lesion. Lagged cross-correlation analysis with reference to the global grey matter signal was performed for each voxel over the range ± 4 repetition times (± 8 s):

$$C_i(\tau) = (1/n_\tau) \sum_t \left[\frac{g(t) \cdot s_i(t+\tau)}{\sigma_{s_i}\ \sigma_g} \right], \quad (1)$$

where g is the grey matter signal, s_i is the signal in voxel i, and σ_{s_i} and $\sigma_g$are the standard deviations of the two signals. The summation runs over frames indexed by t, and n_τ is the number of frames included after a shift of τ (-8 s to $+8$ s). To determine the shift that maximizes the cross-correlation function at a temporal resolution finer than one repetition, the lag (τ) corresponding to the maximum of $C_i(\tau)$ was identified. $C_i(\tau)$ at this lag, as well as one step forward and backward, were fit with a parabolic function and the peak value, $C_i(\tau^m)$, and corresponding temporal shift (τ^m) were computed. Positive and negative values of τ^m correspond, respectively, to a lag or lead relative to the mean grey matter signal. The lag measure, τ^m, was computed for every voxel within the regions of interest. Then, we calculated the lag score of each network i.e. DAN and motor network, by averaging the lag score of all regions of interest e.g. left frontal eye field, left superior parietal lobule etc. In all analyses linking the behavioural deficit with FC, we added the lag measure as a covariate in the model that estimated FC–behaviour correlation. Hence the effects of lag were removed from the computations. This procedure is described in full in Siegel *et al.* (2015).

Lesion segmentation

The lesions were manually segmented using Analyze biomedical imaging software (www.mayo.edu) system by inspection of the T_1-weighted, T_2-weighted, and FLAIR structural images, simultaneously displayed in atlas space. All segmentations were reviewed by two neurologists (M.C. and Alex Carter, MD), with special attention to distinguishing lesion from CSF and haemorrhage from surrounding vasogenic oedema. A voxel-wise map of the lesion distribution in the RHD group ($n = 44$) is shown in Fig. 1A. The average lesion volume was 18 993 mm^3 (SD = 23 050; see Table 1)

Identification of regions in dorsal attention and motor networks in young controls

Our previous work had defined 10 resting state networks containing 169 regions of interest from the young control subjects (Hacker *et al.*, 2013). The 10 networks included the DAN and motor network, as well as eight others that are not relevant to the present paper (visual foveal representation, visual periphery representation, auditory, ventral attention, cingulo-opercular, language, frontoparietal and default mode). The procedure for the construction of the 169 regions of interest has been fully described in earlier publications (Hacker *et al.*, 2013; Baldassarre *et al.*, 2014). Briefly, for each resting state network, provisional regions of interest of 6 mm radius were initially selected from a set of foci derived from either a meta-analysis of in-house task-evoked activation studies or from the literature. These task-related regions of interest were used as seeds to generate whole-brain FC maps by computing the Pearson correlation coefficient r between the region of interest time course and the time courses from all other brain voxels. Next, these maps were averaged over all regions of interest of a network and over subjects to produce 10 provisional network maps. Peak regions from the resulting whole-brain FC maps were identified and consolidated into regions of interest with a 6-mm radius. Finally, each region of interest was assigned to a given resting state network through an iterative process such that the FC topography of a given region of interest was maximally similar to the other regions of interest of the same resting state network and distinct from regions of interest of different networks. Regions of interest exhibiting an inconsistent pattern of FC were considered as 'outliers' and excluded. The analyses in the current paper were confined to the regions of interest in the DAN and motor network, which are listed in Supplementary Table 1. There were 24 DAN

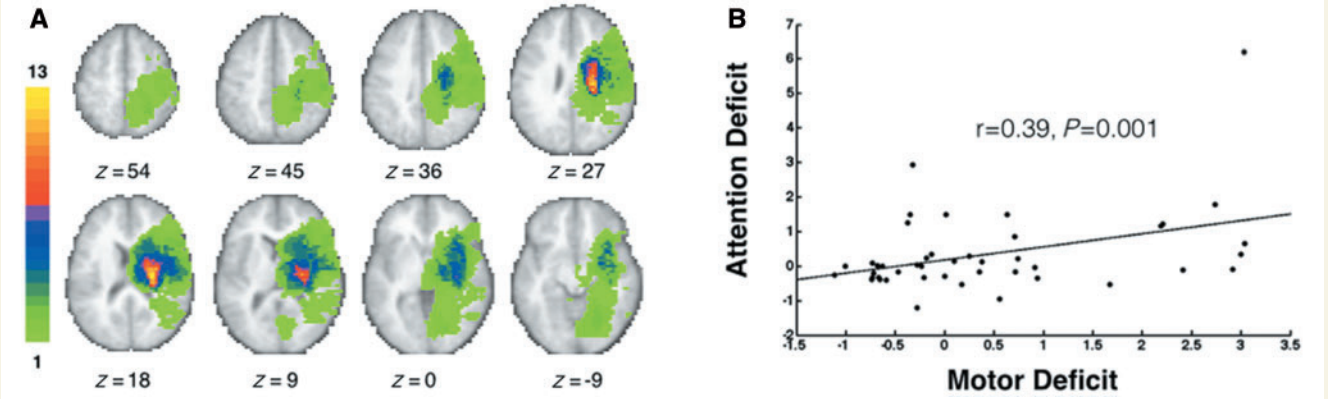

Figure 1 Lesion topography and behavioural results. (**A**) Lesion density in the sample of patients ($n = 44$) for right hemisphere lesions only. The colour bar indicates the number of patients with a lesion in a given voxel. (**B**) The scatter plot displays the correlation between the scores of the motor deficit (upper extremity plus lower extremity) component (x-axis) and attention deficit component (y-axis) from the PCA ($r = 0.39$, $P < 0.001$).

regions of interest, 12 in the left and 12 in the right hemisphere, and 24 motor network regions of interest, 14 in the left and 10 in the right hemisphere.

Computing templates of dorsal attention and motor networks in young control subjects

In the young control subjects, we computed voxel-wise templates of the DAN and motor network using the DAN and motor network regions of interest that were described in the previous section. These templates were used as masks when computing interhemispheric network FC in the stroke patients, as described in the next section. To compute the templates, first, for each subject and each region of interest, we generated a voxel-wise FC map by computing the Pearson correlation coefficient r between the region of interest time course and the time courses from all other brain voxels. Second, we averaged these correlation maps over all regions of interest of a network, e.g. all DAN regions of interest. The r-values in the average map were then transformed to normally distributed scores using Fisher's z. Finally, the single subject maps were averaged across the group to create a template for each network. The final voxel-wise map of the network consisted of all voxels with a $z(r) > 0.3$. Figure 2 shows the group average maps for the motor network and the DAN, with the corresponding regions of interest. Note that the maps include regions that are relatively unique to each network (black voxels for motor network; red voxels for DAN), and regions that are shared between networks. This occurs partly because of spatial proximity of regions of interest, because of individual variability in the precise borders of each network that is then blurred in the group image, and because of true between-network FC. Therefore, we created two masks containing voxels that were relatively unique to the DAN and motor network called the 'DANmask' and 'MNmask', respectively, i.e. the red and black voxels in Fig. 2.

Computing the correlation between deficit and interhemispheric functional connectivity in stroke patients

The primary goal of the present work was to investigate the behavioural specificity of resting FC changes in specific brain networks, the DAN and the motor network, after stroke. For each patient we computed summary FC scores for the interhemispheric FC within the DAN and within the motor network. These summary scores allowed us to quantify and statistically compare the correlations selectively linking attention and motor deficits to specific patterns of interhemispheric FC. Summary scores were computed using the steps 'A' through 'I' displayed in Fig. 3. In the first step (Fig. 3A), for each RHD patient we computed a region of interest-based voxel-wise FC map for each of the DAN and motor network regions of interest. Each map was generated by computing the Pearson correlation coefficient r between the region of interest time course and the time courses from all other brain voxels. The correlation coefficients were Fisher z-transformed prior to further analyses, thereby generating $z(r)$ maps. Overall, for each patient 48 FC maps were obtained, i.e. 12 left DAN regions of interest, 12 right DAN regions of interest, 14 left motor network regions of interest, and 10 right motor network regions of interest. Figure 3A shows in a representative patient, an example of an FC map generated from a left hemisphere region of interest. Although each map was based on a seed in one hemisphere, the map itself indicated the FC of that seed with the whole brain. Importantly, the obtained FC maps did not include any contribution from damaged voxels. Regions of interest falling within the lesions were not considered, and voxels in the FC map falling within the segmented lesion were also excluded from that patient's contribution to the group-level result. In Step 2 (Fig. 3B), for each patient, we averaged the region of interest-based FC maps of each network produced from the seed regions of interest in one hemisphere, e.g. the regions of interest for the left DAN. Step 2 yielded for each subject four network-based z-scored FC maps derived from regions of interest of the left hemisphere DAN, right hemisphere DAN, left hemisphere motor network, and right hemisphere motor network. In Step 3 (Fig. 3C and D), for each subject we applied the DANmask and MNmask (network masks derived from the young controls), respectively, to the left hemisphere and right hemisphere DAN FC maps and left hemisphere and right hemisphere motor network FC maps that were computed in Step 2. The masks were applied in the hemisphere opposite the hemisphere of the seed regions of interest to isolate interhemispheric FC. For instance, for the

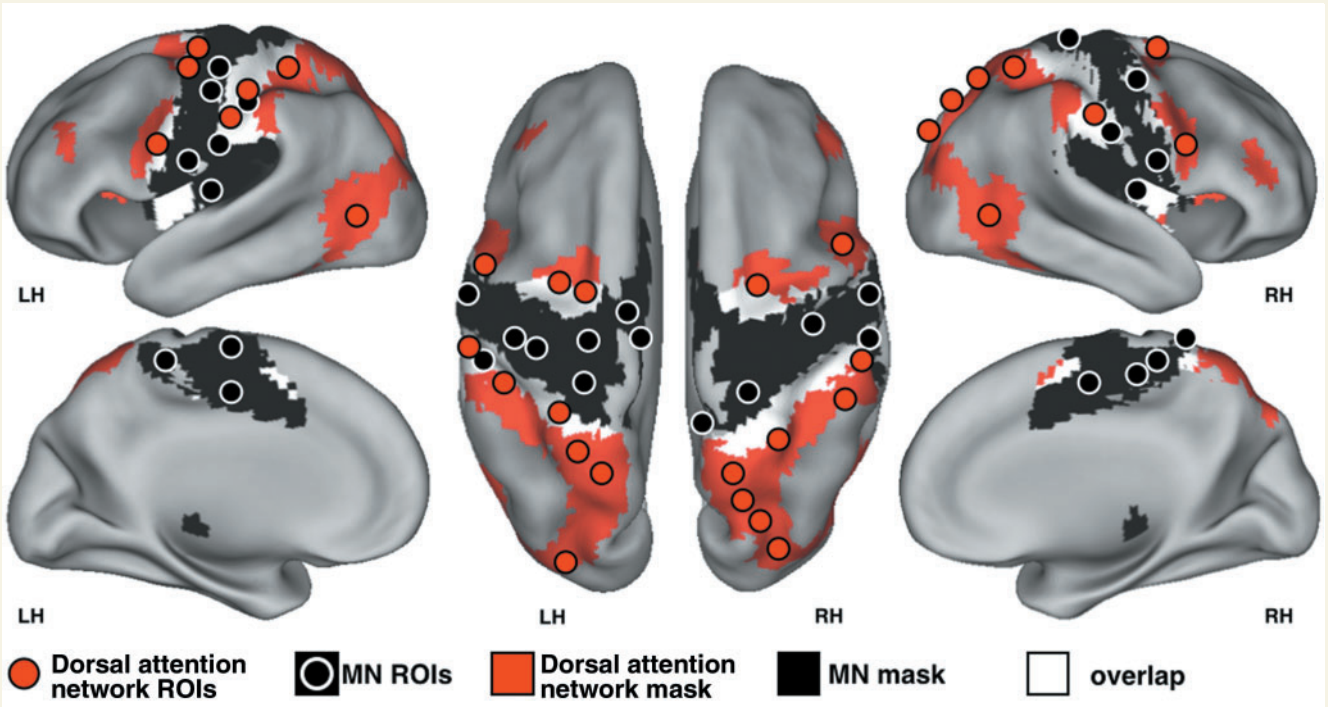

Figure 2 Dorsal attention and motor networks. Lateral, dorsal and medial view of dorsal attention (DAN) and motor (MN) networks projected onto an inflated representation of the PALS (population-average, landmark, and surface-based) atlas (Van Essen, 2005). Voxels in red and black belong to the dorsal attention and motor network, respectively. Voxels in white indicate the overlap between the dorsal attention and motor networks. Circles indicate the regions of interest (ROIs) belonging to the dorsal attention (red) and motor networks (black). RH = right hemisphere.

network-based FC map created from left DAN seed regions of interest, the DANmask was applied to voxels in the right hemisphere. The resulting map (Fig. 3D) indicated the interhemispheric FC between left DAN regions of interest and right DAN voxels. The same procedure was conducted for the FC maps generated from right hemisphere seed regions of interest (Fig. 3E–H). In Step 4, the final within-network summary FC scores were computed by averaging the z(r) values over hemispheres. For example, the interhemispheric FC summary score for the DAN, shown in Fig. 3I, was the average of the z(r) values from the right hemisphere map in Fig. 3D and the left hemisphere map in Fig. 3H. The same steps that were used to examine FC in the DAN for one sample case (Fig. 3A–I) were also applied to examine FC in the motor network for each case. The results for a single case showing the correlation of the interhemispheric FC for the motor network are provided in Fig. 3J. The two summary FC scores for the dorsal attention network and the motor network are hereafter defined as 'DAN FC' and 'motor network FC', respectively. In Step 5, we correlated across patients each summary FC score with each behavioural deficit score, resulting in a 'total' correlation coefficient. However, because the motor and attention deficits are correlated and motor network FC and DAN FC are correlated, we also used partial correlation to identify the selective relationship between the FC of each network and a behavioural deficit. Therefore, in Step 6 we computed the partial correlation coefficient between a network and a behavioural deficit, statistically removing the contribution of the other behaviour (motor deficit or attention deficit) and the FC derived from the other network (DAN FC or motor network FC). For example, we computed the selective association of the DAN with the attention deficit by statistically removing the contribution of the motor deficit and FC in the motor network (see Fig. 3K, which displays FC-behaviour partial correlation of simulated data for the whole sample, $n = 43$). Finally, to control for delays of the haemodynamic response due to a stroke, the averaged lag scores for each network, described above, were statistically removed from the computation of the partial correlation coefficients.

The factorial combination of two behavioural deficits and two summary FC scores resulted in four FC-behaviour partial correlation coefficients. These coefficients were statistically compared by using Structural Equation Models (Preacher, 2006) implemented in the software LISREL (Jöreskog and Sörbom, 1996). Framed in the Normal Theory, correlation coefficients were considered as parameters of the structural equation model and the hypothesis about their equivalence was considered as difference tests computed with the χ^2 statistic (Preacher, 2006). For each pairwise comparison between partial correlation coefficients the χ^2 and its relative significance (P-value) were calculated and corrected for false discovery rate (FDR; Benjamini and Hochberg, 1995) at $\delta = 0.05$.

Importantly, the behavioural significance of FC as computed by the above procedure was determined entirely within a group of stroke patients rather than by comparisons between patients and healthy controls. This procedure mitigated general

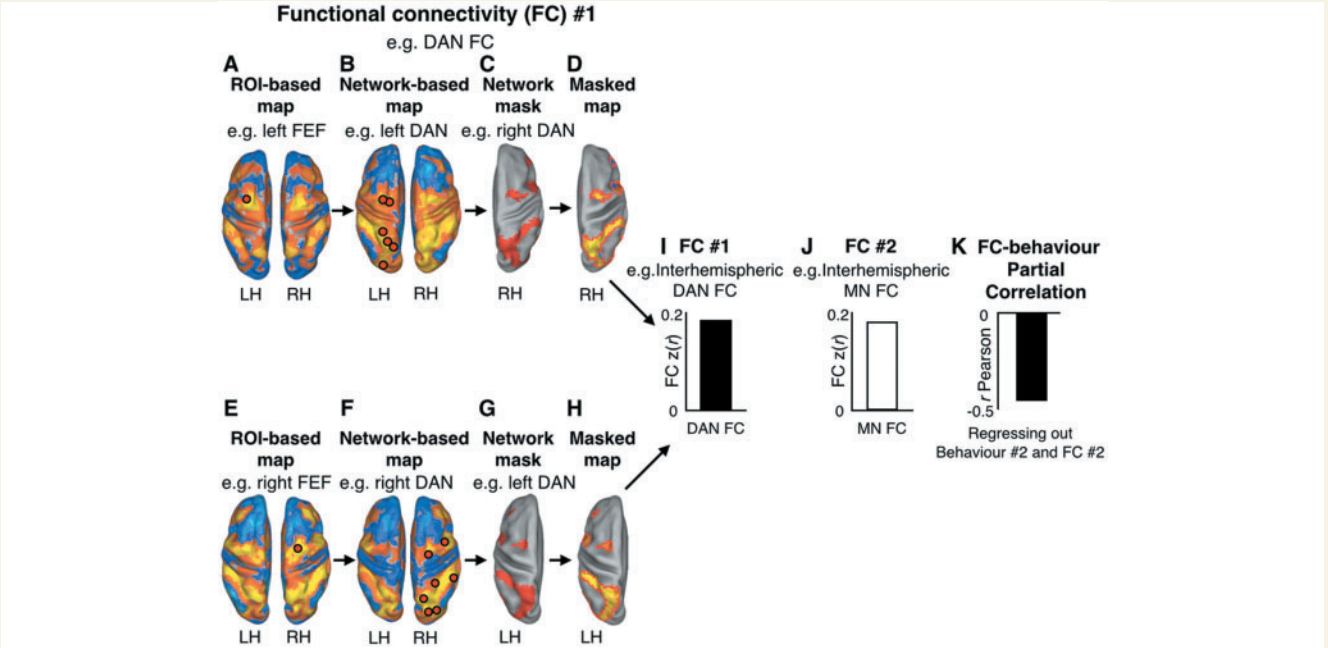

Figure 3 Flowchart of steps involved in computing partial correlation between behavioural deficit and interhemispheric FC. The figure displays the pipeline for computing the four interhemispheric FC-behaviour partial correlation scores (see 'Materials and methods' section). (**A–J**) Panels display real data and refer to a single patient, **K** shows simulated data rather than real data and refers to the whole sample (n = 43). **A** shows the dorsal view of a single patient voxel-wise functional connectivity (FC) map derived from a region of interest (ROI), e.g. left frontal eye field (L FEF, red circle), belonging to the left dorsal attention network (DAN). Orange-yellow colours indicate voxels with positive FC with the region of interest; blue-cyan colours indicate negative FC. LH = left hemisphere; RH = right hemisphere. (**B**) The dorsal view of a single-patient network-based FC map obtained by averaging the region of interest-based FC maps of the left DAN. Colour scale and labels as in **A**. Panel **C** displays a network mask retaining voxels (relatively) uniquely belonging to the right DAN, i.e. DAN_{mask} (red colour). **D** shows the single-patient network-based FC map (i.e. left DAN, **B**) masked with the network mask (derived from young controls, explained in 'Materials and methods' section) displayed in **C**. Accordingly, the map shows the values of FC between the left DAN regions of interest and the target voxels (relatively) uniquely belonging to the DAN in the right hemisphere. Colour scale and labels as in **A** and **B**. (**E–H**) The same procedure as in **A–D** is illustrated, starting from a region of interest of the right hemisphere e.g. right frontal eye field (**E**) and applying the network mask in the left hemisphere e.g. left DAN_{mask} (**G**). Colour scale and labels in **E–F** and **H** as in **A**, **B** and **D**. (**I**) The interhemispheric summary FC is shown of the DAN obtained by averaging the FC scores over the voxels retained within the masked maps in **D** and **H**. Panel **J** displays the functional connectivity (FC) #2. The white bar indicates the interhemispheric summary FC of motor network, obtained in a representative patient. Panel **K** displays simulated data of the partial correlation coefficient obtained by correlating Behaviour #1, e.g. attention deficit for all patients (n = 43), and the interhemispheric FC summary score of DAN (**I**), statistically removing effects of Behaviour #2, e.g. motor deficit and FC #2 (**J**) derived from the motor network.

factors associated with strokes *per se*. Another important aspect of the procedure was that structurally damaged voxels were masked out and did not contribute to the measured FC. Finally, effects of haemodynamic lag were controlled.

Results

Behaviour

Summary scores for the measures from the motor and attention battery were computed using a Principal Component Analysis (PCA), initially conducted on the whole sample (n = 85) comprising both right and left hemisphere damaged patients. The PCA on the motor battery indicated that two factors accounted for 75% of the variance of the behavioural scores: a 'left motor' and a 'right motor' factor corresponding to deficits of the upper and lower extremities of the left and right body, respectively. We defined impairment as a factor score 2 SD below the mean factor score for healthy, age- and education-matched controls. Of patients, 44.6% showed motor impairments, and of these, 50% showed impairment of the left body and 50% of the right body.

The PCA of the attention battery yielded three factors accounting for 68% of the variance. The first factor, accounting for 31% of the variance loaded heavily on measures of visuospatial bias. For example, this factor loaded heavily on the visual field effect from the Posner Cueing Task, with more targets missed in the left as compared to the right visual field for RHD patients and more targets missed in the right as compared to the left visual field for LHD patients. The first factor also loaded on measures indicating a deficit of general attention, such as long

average reaction times averaged over left and right hemifields. When impairment is defined as a factor score 2 SD below the mean factor score for healthy age-matched controls, 24.7% of patients (21 of 85) showed 'neglect'. Separate analyses of patients with left and right hemisphere damage (LHD, RHD) indicated that 76% (16 of 21) of RHD, and 24% (5 of 21) of LHD patients had neglect. In contrast, motor deficits were equally likely following right and left hemisphere lesions. Fifty per cent of patients with motor impairment had RHD and 50% had LHD. Importantly, there was a significant correlation between the scores derived from motor and attention tests in both RHD (Fig. 1B; r = 0.39, $P < 0.001$) and LHD (r = −0.32, $P < 0.05$) patients. The different signs of the correlation for RHD and LHD patients reflects the fact that visual field bias was positive for RHD patients and negative for LHD patients.

Because of the small number of LHD patients with attentional deficits, the analysis of the relationship between FC and motor and attention deficits was restricted to the RHD patients. The two behavioural factors used for the FC–behaviour analyses are hereafter called 'motor deficit' and 'attention deficit', where the former captured deficits of upper and lower left extremities, while the latter described spatial and non-spatial attention deficits.

A double dissociation of networks and behaviour

To investigate the behavioural specificity of changes in resting state FC after stroke, we correlated across all RHD patients the scores for a given behavioural deficit with the scores for interhemispheric FC within a given network. Four correlations were computed, determined from the factorial combination of two behavioural deficits, attention and motor, and two networks, the DAN and motor network.

We took into account correlations between the attention deficit and motor deficit and between FC in the DAN and motor network by computing partial correlations. For each partial correlation between a behavioural deficit and the interhemispheric FC for a given network, we regressed out the contribution of the other behavioural deficit, and the FC derived from the other network. Therefore, each partial correlation indicated the unique relationship between the interhemispheric FC of a single network and a single behavioural deficit.

Figure 4 displays the partial correlation coefficients for each network and behavioural domain. Supplementary Table 2 shows the results for total correlation coefficients. The figure indicates that only the FC-behaviour partial correlations linking a behavioural deficit with the FC derived from the corresponding network were significant i.e. attention deficit and DAN FC (bar 1, r = −0.52, $P = 0.0004$) and motor deficit and motor network FC (bar 4, r = −0.36, $P = 0.015$), indicating that severe deficits in a given

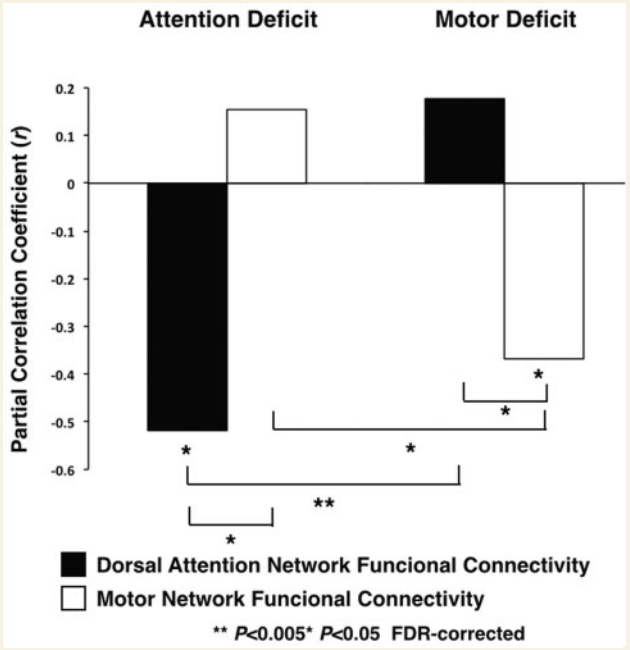

Figure 4 Partial correlations between behavioural deficits and interhemispheric FC. The bar graph plots four FC-behaviour partial correlation coefficients (*r* Pearson) derived from the interhemispheric FC of the DAN (black) and motor network (white). Bars 1–2 and 3–4 indicate correlations involving the attention deficit and motor deficit, respectively. Each correlation coefficient, e.g. bar 1, is obtained by correlating a given behaviour, e.g. attention deficit, with the FC derived from a given network, e.g. DAN FC, by statistically removing the other behaviour, e.g. motor deficit, as well as the FC derived from the other network, e.g. the motor network FC.

cognitive domain were associated with low interhemispheric FC of the corresponding network. By contrast, the FC-behaviour partial correlation between a deficit e.g. attention, and the FC of the non-corresponding network, e.g. motor network, was not statistically significant and was nominally positive, meaning that high deficit corresponded to high interhemispheric FC. Importantly, Structural Equation Modelling indicated that the magnitude of the partial correlation coefficient involving the attention deficit was significantly larger for DAN FC than for motor network FC [bar 1 versus bar 2; $\chi^2(1) = 6.56$, $P = 0.01$, corrected for FDR at $\delta = 0.05$]. Conversely, the magnitude of the partial correlation coefficient related to the motor deficit was significantly larger for motor network FC than for DAN FC [bar 4 versus bar 3; $\chi^2(1) = 3.91$, $P = 0.047$, corrected for FDR at $\delta = 0.05$].

We also compared the partial correlation scores grouped within each network. The magnitude of the partial correlation coefficient involving DAN FC was significantly higher for the attention deficit than the motor deficit [bar 1 versus bar 3; $\chi^2(1) = 8.95$, $P = 0.002$, corrected for FDR at $\delta = 0.05$], while motor network FC was more correlated with the motor deficit than the attention deficit [bar 4

versus bar 2; χ^2 (1) = 4.62, P = 0.031, corrected for FDR at δ = 0.05].

These findings indicate a double dissociation linking a given behavioural deficit e.g. attention, to the FC derived from the corresponding network, e.g. DAN FC.

Control analyses

Because most patients in the sample had ischaemic strokes, with a smaller number having haemorrhagic strokes, we confined the analysis to the ischaemic patients. Similar to the whole sample, the PCA on the behavioural scores yielded attention deficit and motor deficit factors. Structural Equation Modelling revealed that the attention deficit was significantly more correlated with DAN FC than motor network FC [$\chi^2(1) = 5.65$, $P = 0.017$], while the motor deficit exhibited a significantly higher correlation with motor network FC than DAN FC [$\chi^2(1) = 4.05$, $P = 0.043$], comparisons corrected for FDR $\delta = 0.05$. Hence, the double dissociation was maintained. We also conducted the main analyses after removing a patient who had a very large attention deficit as well as a large motor deficit (see scatterplot in Fig. 1). As in the whole group, attention deficit and motor deficit factors were detected. Structural Equation Modelling indicated a double dissociation in which the attention deficit was more correlated with DAN FC than motor network FC [$\chi^2(1) = 3.99$, $P = 0.045$] and the motor deficit was more correlated with motor network FC than DAN FC [$\chi^2(1) = 4.13$, $P = 0.042$], but only at a significance level that was not FDR-corrected. Finally, a correlational analysis revealed that lesion size (Table 1) modestly correlated with the motor deficit (r = 0.35; $P = 0.01$), and marginally correlated with the attention deficit (r = 0.28; $P = 0.06$). Correlations were not greatly affected by removing haemorrhagic patients (motor deficit: r = 0.36; $P = 0.01$; attention deficit: r = 0.28; $P = 0.08$).

Although several studies have shown that the topography of resting state networks, including the DAN and motor network, is maintained during sleep (Larson-Prior *et al.*, 2009), we assessed the effects of sleepiness during the functional MRI scan on the double dissociation. At the end of the scanning session, patients were asked: 'During the scan, how much of the time did you feel sleepy?' Their answer was given on a 5-point Likert Scale going from 'none of the time' (0%) to 'all of the time' (100%). The seven patients who reported high levels of sleepiness during the MRI scan were almost equally distributed between the three groups with behavioural deficits: two showed only an attention deficit, two showed only a motor deficit, and three showed both attention and motor deficits. To control for variations in sleepiness, we regressed out from the FC-behaviour correlations the scores obtained in the sleep questionnaire. This analysis indicated that the attention deficit was more correlated with DAN FC (r = −0.5; $P = 0.001$) than motor network FC [r = 0.15; $P = 0.4$; $\chi^2(1) = 5.97$, $P = 0.014$; corrected for FDR at $\delta = 0.05$], while the motor deficit was more correlated with motor network FC (r = −0.3661; $P = 0.015$) than DAN FC (r = 0.1862; $P = 0.25$) [$\chi^2(1) = 3.997$, $P = 0.04$; corrected for FDR at $\delta = 0.05$]. Hence, these findings indicate that the double dissociation was not affected by sleepiness during the scan.

Discussion

The results demonstrated a double dissociation linking particular behavioural deficits to abnormal FC in particular networks. The attention deficit, a measure that included left-field neglect and poor general performance, was significantly more correlated with interhemispheric FC in the DAN than motor network. Conversely, the motor deficit, a measure of motor impairment of the left upper and lower extremities was significantly more correlated with interhemispheric FC in the motor network than DAN. These results were obtained with procedures that ensured that structurally damaged voxels did not contribute to FC and that controlled for haemodynamic lag. To our knowledge, these results show the first double dissociation of behavioural deficit and network for abnormal resting FC following stroke.

Reduced interhemispheric functional connectivity for motor and attention deficits

A number of studies have reported that following a stroke, abnormal resting FC is associated with motor deficits (Carter *et al.*, 2010, 2012*a*; Wang *et al.*, 2010; Park *et al.*, 2011; van Meer *et al.*, 2012; Yin *et al.*, 2012; Chen and Schlaug, 2013; Golestani *et al.*, 2013; Bauer *et al.*, 2014) and unilateral spatial neglect (He *et al.*, 2007; Carter *et al.*, 2010; Baldassarre *et al.*, 2014). The most commonly reported correlate at the acute or subacute stage is a reduction in interhemispheric FC. Because of the vascular distribution of MCA strokes, however, stroke-induced lesions may produce both motor deficits and neglect. In the current sample of RHD patients, the correlation of motor deficit scores and attention deficit scores was r = 0.39 ($P = 0.001$). The results show that resting interhemispheric FC is related to each deficit even after regressing out effects of the other deficit.

The double dissociation was demonstrated for patients with right hemisphere lesions, who are more likely to show neglect than patients with left hemisphere damage (Weintraub and Mesulam, 1987; Stone *et al.*, 1991). Given this hemispheric asymmetry, it may seem surprising that the interhemispheric FC of both right and left hemisphere DAN regions was correlated with neglect (He *et al.*, 2007; Carter *et al.*, 2010; Baldassarre *et al.*, 2014). Neglect is thought to result in part from unbalanced DAN activity even though the right hemisphere lesions causing neglect often do not directly damage the DAN (Husain and

Kennard, 1996; Karnath *et al.*, 2001, 2009; Mort *et al.*, 2003). In previous work we proposed that unbalanced DAN activity is more likely following RHD than LHD because the former directly affects right lateralized networks for arousal and reorienting that interact strongly with the DAN (Corbetta and Shulman, 2011). These between-network interactions may normally occur via white matter fronto-parietal tracts such as the second branch of the superior longitudinal fasciculus that are damaged in neglect patients (Thiebaut de Schotten *et al.*, 2014; Corbetta *et al.*, 2015). Therefore, right lateralized neglect is not inconsistent with the involvement of bilateral networks such as the DAN.

Behavioural deficits link with resting functional connectivity of corresponding networks

Part of the promise of FC measurements in stroke patients is that physiological dysfunction of particular brain networks is most strongly related to particular behavioural deficits. For this reason, it is important to demonstrate that correlations between behavioural deficits and network FC can be doubly dissociated. Double dissociations would seem most easily achieved for behaviours that involve partly or mostly separable brain systems and differential hemispheric lateralization, such as language and spatial attention. A previous study (Nomura *et al.*, 2010) demonstrated that a lesion damaging the regions of interest of one of two cognitive control networks produced greater FC decreases within the damaged than undamaged network, but did not show a selective association between that damage and particular behavioural deficits. In fact, we are not aware of a previous study that has demonstrated a double dissociation in correlations for any pair of networks and behavioural domains following stroke.

In the present work, attention deficits and motor deficits of the left upper and lower extremities involved brain systems in the right hemisphere that partly occupied neighbouring patches of brain tissue. Therefore, it was striking that a double dissociation was observed for the correlations between motor and attention deficits and FC in the motor network and the DAN. Moreover, the linkage of specific networks with particular behavioural domains was consistent with the presumed functional roles of those networks, e.g. the motor network and motor function. Therefore, these results strongly support the behavioural specificity of resting FC. Different network-specific patterns of resting FC are associated with different behavioural deficits.

The current findings contrast with those from the only previous study that examined multiple behavioural deficits and brain networks following stroke. Carter *et al.* (2010) reported that motor deficits were equally associated with interhemispheric FC of the motor network and DAN, with no evidence of a greater association with the motor network. Conversely, attention deficits only showed a non-significant trend toward a greater correlation with the interhemispheric FC of the DAN than the motor network. The different results likely reflected several methodological features of the current study. We used a partial correlation technique that identified the unique relationship between a behavioural domain and FC for a particular network. We also partitioned the motor network and DAN into topographic components that were relatively unique. Finally, our sample ($n = 43$) was larger than that of Carter *et al.* (2010), which included 23 patients, 16 with behavioural measurements in both the attention and motor domains. Baldassarre *et al.* (2014) showed that FC–behaviour correlations involving spatial neglect were highest in the DAN, motor network, and auditory networks, with smaller correlations in less related networks such as language. However, as only a single behaviour was examined, the behavioural specificity of the abnormal FC could not be determined. Similarly, to our knowledge, all previous studies relating abnormal FC to behaviour following stroke have focused on a single behavioural domain.

Previous work has demonstrated a correspondence in healthy subjects between resting state inter-regional correlations and task-driven coactivations (Smith *et al.*, 2009). This correspondence reflects in part a dependence of both on anatomical connectivity (Sporns, 2013). But the fact that resting state FC can be modified over relatively short time periods by performing a task has suggested that resting state interactions between brain regions also reflect the frequency and past history of coactivation (Albert *et al.*, 2009; Hasson *et al.*, 2009; Lewis *et al.*, 2009; Tambini *et al.*, 2010). Conversely, the resulting pattern of spontaneous interactions at rest influences subsequent task performance (Baldassarre *et al.*, 2012). These results have suggested a reciprocal relationship (Lewis *et al.*, 2009; Baldassarre *et al.*, 2012) in which task-induced activity modifies spontaneous activity (Albert *et al.*, 2009; Hasson *et al.*, 2009; Lewis *et al.*, 2009; Tambini *et al.*, 2010), which in turn shapes and constrains task-induced activity and behaviour (Fox *et al.*, 2007; Hesselmann *et al.*, 2008; Sadaghiani *et al.*, 2009). The present observation that network-specific patterns of resting FC are associated with corresponding behavioural deficits supports the overall hypothesis that resting state organization constrains task-driven behaviour. A possible corollary is that post-stroke interventions that restore normal patterns of resting FC may be associated with good recovery.

Limitations

The double dissociation was observed between different behavioural domains (attention, motor) and networks (DAN, motor network), but FC–behaviour associations might also be present that link components within a domain (e.g. egocentric versus allocentric neglect; Medina *et al.*, 2008) to different networks or sub-networks. The current study involved a prospective group of stroke patients for whom behavioural deficits were correlated (Corbetta *et al.*, 2015).

Finer FC-behaviour dissociations might be observed for highly selected patient samples that weighted, for example, different neglect components.

The double dissociation relating FC to behaviour was only demonstrated for patients with RHD as this group included a sufficient number of patients with motor and attentional deficits.

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Supplementary material

Supplementary material is available at *Brain* online.

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