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Ventral attention and motor network connectivity is relevant to functional impairment in spatial neglect after right brain stroke

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Abstract

Emerging research suggests spatial neglect after right stroke is linked to dysfunctional attention and motor networks. Advanced functional connectivity analysis clarified brain network recovery, however we need to know how networks participate in adaptive motor performance. We need to verify network changes associated with validated functional measures and spatial-motor performance in spatial neglect, especially in patients with large brain lesions and significant disability. This study tested whether disability-relevant spatial neglect associates with different patterns of resting state functional connectivity between motor, dorsal and ventral attention networks (MN, DAN and VAN). Right stroke patients had spatial neglect (n = 8) or not (n = 10) on the Behavioural Inattention Test-conventional. Spatial neglect patients had weaker intranetwork VAN connectivity, and reduced internetwork connectivity between VAN and left frontal eye field (DAN), and between VAN and the left primary motor area (MN). These network impairments might explain the co-occurrence of attention and motor deficits in spatial neglect, and open a path to assessing functional connectivity in clinical trials of combined spatial retraining and motor rehabilitation after stroke.

Keywords

Spatial neglect; Stroke; Motor network connectivity; Attention network connectivity; Machine learning

1. Introduction

Spatial neglect is defined by asymmetric spatial performance in a subject with a brain lesion, associated with functional disability (Barrett & Burkholder, 2006). These patients fail to report, respond, orient or act contralesionally (Adair & Barrett, 2008; Barrett & Muzaffar, 2014; Heilman, Watson, & Valenstein, 1979). Abnormally asymmetric motor-intention and

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bandc.2018.11.013.

movement in spatial neglect is termed spatial Aiming neglect (Goedert, Chen, Boston, Foundas, & Barrett, 2014). This deficit is probably the human manifestation of spatial neglect-associated spontaneous rotation and asymmetric posture in animal models across the mammalian class (Barrett & Muzaffar, 2014; Deuel & Collins, 1984; Marshall & Ridley, 2003; Marshall, 1979; Ungerstedt, 1971; Watson et al., 1974, 1978; Zimmerberg, Glick, & Jerussi, 1974). Clinicians typically classify spatial neglect as a visual problem, and thus separate spatial from motor programs of therapy. They may also misinterpret the abnormal, asymmetric functional movements typically resulting from spatial neglect as the result of problems with visual perception, directly contrary to studies demonstrating that spatially-biased movements cause errors, and not biased perception (Hoyman, Weese, & Frommer, 1979; Valenstein, Heilman, Watson, & Van Den Abell, 1982; Watson, Miller, & Heilman, 1978), or fundamental motor processes (Deuel & Collins, 1984; Deuel, 1992). Thus, despite clear evidence that spatial neglect affects movement and balance (Shiraishi, Muraki, Ayaka Itou, & Hirayama, 2010; Ten Brink, Verwer, Biesbroek, Visser-Meily, & Nijboer, 2017), increases fall risk (Alemdaroğlu, Uçan, Topçuoğlu, & Sivas, 2012; Chen, Chen, Hreha, Goedert, & Barrett, 2015), predicts chronic problems with community mobility (Oh-Park, Hung, Chen, & Barrett, 2014) and appears to suppress paralysis recovery (Nijboer, Kollen, & Kwakkel, 2014), spatial retraining is not used in standard motor rehabilitation.

A knowledge gap in the neurophysiology of spatial and motor system interaction may contribute to the treatment gap in spatial retraining for motor disability. Patients with spatial neglect, who are strong enough to tolerate intense treatment, still execute asymmetric movements; their spatial Aiming errors result in inadequate or inconsistent motor effort, preventing them from engaging in optimally-in- tensive motor training (Vallar, Guariglia, Nico, & Pizzamiglio, 1997). Decreased motor effort is demonstrated when they make movements toward the neglected space, or on the neglected side of the body. Abnormal motor effort may also be observed in decreased force exerted, force sustained, amplitude, speed, or frequency of movements, or in other movement parameters such as directional motor response inhibition (Barrett, Schwartz, Crucian, Kim, & Heilman, 2000; Butter, Rapcsak, Watson, & Heilman, 1988; Heilman, 2004). If spatial retraining improved motor effort, it could improve motor recovery out-comes. However, many patients with spatial neglect receive no evidence-based spatial retraining focused on adaptive movement. Instead, these patients may receive treatment designed exclusively to improve visual awareness.

Baldassarre et al. (2014) reported changes in synchronized activity of multiple brain regions associated with a particular function, when patients have a clinical deficit. They demonstrated that spatial neglect was associated with decreased interhemispheric brain network functional connectivity of the dorsal attention network, in which activity may determine whether patients manifest spatial neglect (Corbetta & Shulman, 2011). Baldassarre et al. (2014) also demonstrated large-scale changes in functional connectivity associated with spatial neglect. They demonstrated altered connectivity of attention systems with multiple brain systems in spatial neglect, including connectivity of dorsal attention with motor systems. In a further study, Baldassarre et al. (2016) focused specifically on attention and motor systems, and demonstrated that behavioral attention deficits were associated with decreased synchronized activity of decreased functional connectivity of dorsal attention networks. Motor deficits were associated with decreased functional connectivity of motor networks. Thus, synchronized activity of both large-scale and specialized brain networks appears to be altered in spatial neglect, and the synchronized activity in both dorsal attention networks and motor networks may be linked to stroke-related deficits. Siegel et al. (2016) examined how lesion location versus functional connectivity could predict attention, motor, and other behavioral deficits. These authors demonstrated that either lesion topography or dorsal attention network functional connectivity could predict attention deficits, however, they found that lesion topography was a better predictor of motor deficits. Lastly, Ramsey et al. (2016) demonstrated that interhemispheric connectivity of attention networks was associated with spatial neglect recovery. These authors also demonstrated altered connectivity of attention networks and other brain regions, including regions important to motor network function, associated with spatial neglect recovery. Although this study suggests that abnormal internetwork attention-motor connectivity may be associated with spatial neglect, it is not yet clear in these four studies how function of the ventral attention network, potentially critical in inducing spatial neglect (Corbetta & Shulman, 2011), relates to motor network function. Further, none of this research specifically identified how inter-network interaction between brain systems specialized for attention and movement are associated with the spatial neglect symptoms that cause disability. This is partly due to the focus of these studies on attention networks, and not on attention-motor interaction. However, these studies also used laboratory-based impairment assessments, which are not valid predictors of disability, especially in moderately-impaired patients.

These studies also did not clarify how brain network interaction can be broadly applied in spatial neglect research. In order to avoid confounding functional activation analyses with abnormal activation caused by brain dysfunction, previous studies excluded subjects from analysis who had lesions in brain regions participating in the cortical networks under study. Thus, group-level analyses did not include all of the subjects with spatial neglect. Patients with large lesions, who represent typical stroke patients with spatial neglect and hemiparesis receiving care in inpatient settings, were likely to be excluded, because their brain lesions were more likely to include network nodes. The investigator teams in these studies also used multiple brain regions to calculate network interaction (more than 150 in each of these studies), examined multiple brain networks (7 or more), and performed both group-level and subject-specific evaluations of the neuroimaging data. This ensured that subject-specific differences in brain network topography (either premorbid, or based on brain lesion location) had a minimal influence on their neuroimaging analyses. However, these multi-step, individualized analyses may not be practical for use over multiple sites by clinical trial investigators. If researchers lack the time and radiologic specialization to specify networks in a data-driven fashion, they may prefer to use methods that pre-specify regions participating in brain networks (Lee, Smyser, & Shimony, 2013).

In this study, we wished to address the above knowledge gaps in spatial-motor brain network interaction. We wished, first, to investigate whether both dorsal and ventral attention-motor network interactions explain an adverse effect of spatial neglect on functional performance. Second, we wished to study disability-relevant measures of spatial neglect. Third, for this analysis to be relevant to patients with the greatest motor disability and need for acute and post-acute care (Cipriano, Steinberg, Gazelle, & González, 2009), we set out to include patients with large brain lesions, and moderate to severe deficits, who were probably not represented in previous study groups. Also, we sought to determine if the association of attention and motor network co-activation has predictive validity for assigning patients to neglect positive and neglect negative groups. To this end, we validated our findings using hierarchical clustering and a leave-one-out neural network classifier.

2. Method

2.1. Participants

The participants were 18 volunteers (8 women, 10 men, ages 30–73, $M = 57$) with a diagnosis of right-brain stroke, who underwent inpatient rehabilitation at Kessler Institute for Rehabilitation (see Table 1 for participant characteristics). Participants did not have any prior neurological disorder. Median time post-stroke at the time of study participation was 4.25 weeks (range 1.5–226 weeks). Median stroke lesion volume was 46.18 cm^3 (range 0.56–217.49 cm^3). All participants gave written informed consent prior to participation.

We used the Behavioral Inattention Test-conventional subtest (BIT- c; see Table 1) to classify patients as having, or not having, spatial neglect (Halligan, Cockburn, & Wilson, 1991). Between patients with spatial neglect ($n = 8$) and those not meeting BIT-c criteria for spatial neglect ($n = 10$; Table 1), there was no difference in age ($t = -0.353$, $p > 0.7$, n.s.). However, a t-test comparing lesion volume in patients with (mean = 90.9 cm^3, SD = 72.52) versus those without spatial neglect suggested that lesion volumes tended to be larger in patients with spatial neglect (mean = 32.0 cm^3; $SD = 30.68$; $t = -2.15$, $p = 0.06$, equal variances not assumed), although a nonparametric t-test comparing lesion volume in the groups with and without spatial neglect, performed because of inhomogeneity of variances (Levene's test $F = 3.651$, $p = 0.07$) did not reach significance ($p = 0.15$).

2.2. Materials

All participants completed a demographic and health questionnaire, and spatial neglect testing using the BIT-c as noted above. To improve external validity of neglect classification and disability-relevance, patients were also examined with the Catherine Bergego Scale (Azouvi et al., 1996) via the Kessler Foundation Neglect Assessment Process (KF-NAP™ (Chen, Hreha, Fortis, Goedert, & Barrett, 2012)). Thus, subjects were evaluated for spatial neglect with tests having demonstrated (1) predictive validity in identifying neglect-associated functional disability and (2) utility to measure treatment-related functional performance change (Chen et al., 2015; Di Monaco et al., 2011; Goedert et al., 2014; Mizuno et al., 2011). The BIT-c includes 6 domains of spatial neglect testing (line, letter and star cancellation tasks, figure and shape copying, and representational drawing). Each task is scored for accuracy and the degree of lateralized bias. The KF-NAP (Chen et al., 2015) standardized and clarified the administration of the Catherine Bergego Scale (CBS), a 10-category scale for spatial neglect based on observed activities of daily living (e.g., eating, dressing, grooming, gaze orientation).

2.3. Procedure

Testing was conducted by trained research staff. Participants with a cumulative score of 129 or less (of possible 146 points) were classified on the BIT-c as having disability-relevant spatial neglect (Halligan et al., 1991). For the CBS, although some authorities recommend CBS > 0 indicates functionally-significant spatial neglect (Azouvi et al., 1996; Pitteri et al., 2018), we used a conservative criterion to define spatial neglect, to reduce the influence of evaluator bias (CBS > 5). Test items were scored in accordance with test instructions.

2.4. MRI acquisition

MRI scans were collected on a 3.0T Skyra Magnetom scanner (Siemens) at the Kessler Foundation Rocco Ortenzio Neuroimaging Center. To help segment lesions, high-resolution T1 structural Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) scan (TR = 2100 ms, TE = 3.43 ms, 176 sagittal slices, 1mm^3 voxels) and a T2 Fluid Attenuated Inversion Recovery (FLAIR) scan (TR = 9000 ms, TE = 91ms, 35–50 slices, 1 × 1 × 3–5mm^3 voxels) were acquired from each participant. To assess functional connectivity, resting state functional scans were acquired with a gradient-echo echoplanar imaging (EPI) sequence (TR = 2000 ms, TE = 30 ms, 32 slices, 2.3 × 2.3 × 3 mm^3 voxels).

2.5. Analysis

The behavioral and neuroimaging data were analyzed using SPSS version 21 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.); RStudio using R version 3.4.3 (R Core Team, 2013), and its contributed packages: nnet (Venables & Ripley, 2002) and hclust (Murtagh & Legendre, 2014); AFNI and its associated packages (Cox, 1996); FSL and its associated packages (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012); and ICA- AROMA (Pruim et al., 2015).

2.5.1. Lesion mapping—Lesion mapping was done in a semi-automated fashion using FSLView and fslmaths available as part of FSL library (Jenkinson et al., 2012). High resolution T1-weighted structural and FLAIR images were overlaid onto each other. FLAIR images were thresholded to identify voxels with abnormal intensity. These images were binarized and edited manually to include both areas of stroke core and all surrounding voxels that appeared hyper-intense on the FLAIR scans. Any bilateral, sub-clinical lacunar lesions that appeared on both the T1-weighted and FLAIR images, and contained more than 15 voxels, were mapped as part of the lesion-weighting mask. No participant had a clinically-defined stroke in the left hemisphere (Fig. 1; separate lesion maps are presented for patients with and without spatial neglect in Supplementary Fig. 1).

2.5.2. Resting state functional connectivity preprocessing—Functional Images were motion-corrected using MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002) and brain-extracted using BET (Smith, 2002). Affine transforms were created to align functional scans with structural and 2 mm MNI152_T1_2mm_brain template using FLIRT (Jenkinson & Smith, 2001; Jenkinson et al., 2002) with 6 and 9 degrees of freedom for within-participant and participant-to-template transformations, respectively. Cost function masking of the lesioned areas was used to avoid warping of lesions. Using affine transforms as a starting point, non-linear transforms were computed using FNIRT (Jenkinson et al., 2012) for each participant's functional and structural scans to convert them into a standard 2 mm MNI152_T1_2mm_brain template. Lambda (a regularization parameter) of 200 was used to avoid excessive warping. ICA-AROMA (Pruim et al., 2015) was used for additional motion correction. ICA-AROMA is an Independent-Component Analysis-based strategy for removal of head motion. ICA-AROMA was shown to be superior to motion-parameter regression and spike regression in validation studies (Pruim et al., 2015). The algorithm was applied to the motion-corrected, brain-extracted functional data. The resulting de-noised functional data were transformed using affine and non-linear transformation matrices into the 2 mm MNI152_T1_2mm_brain coordinate space, to enable data aggregation across participants. Lesions were excluded from the computation of functional connectivity maps by masking. Data from all participants were included in the analysis. No participants had a complete lesion of any of the ROI in the right hemisphere.

2.5.3. Resting state functional connectivity analysis—Resting state functional connectivity measures the correlation among brain regions regardless of the direction of influence or modulation by any physical or cognitive task. In this analysis, seed-based to whole-brain resting state functional connectivity of the motor network (MN), dorsal attention network (DAN), and ventral attention network (VAN) was studied using a seed-based correlation method, in which the correlation between the activity of a region of interest (ROI) and all voxels of the brain was calculated.

2.5.4. Regions of interest (ROIs)—The MN was studied using two ROIs in the left and right primary motor cortices (lM1 and rM1 [± 29 −17 56]). Ml ROI coordinates were selected based on an fMRI study (Cunningham, Machado, Yue, Carey, & Plow, 2013), that revealed the functional somatotopy of finger movement based on a complex motor task. Time series were averaged from a ROI with voxels inside a 10 mm radius sphere around the center coordinate in the hand area, this 10 mm radius allowed including both hand and arm areas of the upper extremity somatotopy. Similarly, the DAN was studied using bilateral frontal eye field (lFEF and rFEF [± 28 − 8 52]) areas. Lastly, the VAN was explored using bilateral ventral frontal cortices (lVFC and rVFC [± 42 20 −6]) as regions of interest. Coordinates of FEF and VFC ROIs were used in Farrant and Uddin (2015) to study DAN and VAN networks.

2.5.5. Correlation maps—For each ROI, the mean time-series was calculated by averaging the time series of all voxels inside an ROI. Correlation between each ROI time-series and all voxels in the brain was calculated using AFNI 3dfim + function. The correlation maps of lM1 and rM1 regions were merged to form the MN by averaging. A similar procedure was used to estimate the DAN network using FEF seeds, and VAN using VFC seeds. The correlation maps were converted to Z-score maps using 3dcalc AFNI function for visualization and computing a FDR-corrected group average (Fig. 2). Combining analysis over the left and right networks followed the convention for generating whole-brain network maps (Baldassarre et al., 2014, 2016).

2.5.6. Interhemispheric (intranetwork) connectivity—Fslstats function was used to extract the correlation values for rM1 ROI within the lM1 correlation map, and lM1 ROI within the rM1 correlation map; the average of both maps provided the interhemispheric connectivity measure between lM1 and rM1. This same procedure was used to estimate interhemispheric connectivity between bilateral FEFs and VFCs.

2.5.7. Internetwork connectivity—Fslstats function was used to extract the correlation between ipsi- lesional (right) and contralesional (left) M1, FEF, and VFC with each of the three networks (MN, DAN, and VAN). Calculation of MN, DAN, and VAN networks was described in **Correlation Maps,** above.

2.5.8. Analysis—We conducted a MANOVA with presence of spatial neglect (BIT-c score ≤ 129) as a between-subjects factor, log weeks post stroke and log lesion volume as covariates, and resting state functional connectivity measures as outcome.

To explore the relationship between the disability-relevant BIT-c scores and functional connectivity, we conducted a series of 12 linear regressions. We examined the coupling between BIT-c and connectivity separately in the spatial neglect and non-spatial neglect groups.

Our last set of analyses included hierarchical cluster analysis and a neural network classifier. These analyses were intended to cross-vali- date relationships between our variables of interest estimated in the above general linear model analyses. Both approaches (clustering and classification) conduct multivariate pattern analysis (MVPA). Compared to general linear model analyses, MVPA is better able to estimate covariation of variables and its diagnostic contribution to a condition of interest (Hanson & Halchenko, 2008). Multivariate pattern analysis also allows for a generalization step to add rigor to the conventional general linear model analysis. Multivariate pattern analysis can thus test a generated model by subjecting it to a sort of within- experiment replication, which directly assesses model reliability.

First, a hierarchical cluster analysis was carried out using Euclidean distance metric and Ward's clustering method (Murtagh & Legendre, 2014). Hierarchical cluster analysis uses a multivariate matrix of distances between rows (participants) of an observation table (participants × functional connectivity) to build similarity-based clusters. This is done by considering a single observation as a candidate for cluster membership using a clustering method. Ward's agglomerative clustering method produces groups that minimize within-group variability at each binary fusion. The connectivity data used in this analysis included 9 correlation measures for interhemispheric connectivity (MN, DAN, VAN, MN left to right, MN right to left, DAN left to right, DAN right to left, VAN left to right, VAN right to left) and 15 measures of internetwork connectivity (these included global internetwork connectivity: MN to DAN, MN to VAN, DAN to VAN, and each network connectivity to the seeds of the other network: MN to lFEF, MN to rFEF, MN to lVFC, MN to rVFC, DAN to lM1, DAN to rM1, DAN to lVFC, DAN to rVFC, VAN to lM1, VAN to rM1, VAN to lFEF, VAN to rFEF). In this analysis, we compared machine-generated categorical classification of "neglect" versus "non-neglect" groups using both the BIT-c score cutoff, and the performance-based CBS via KF-NAP (KF-NAP). Next, we trained a neural network classifier to predict the presence of spatial neglect (defined by BIT-c score ≤ 129), using the functional connectivity data. The key feature of this analysis is that not only can it fit a model to the data, but it can also validate the model on new untrained observations. The same 24 connectivity measures from the cluster analysis were used as a starting point in this analysis. A principal component analysis was conducted on the connectivity measures to reduce the number of correlated dimensions into orthogonal variance components. The first 3 principal components, which accounted for 83% of total variance, were used to train the classifier. The 10-hidden unit neural network classifier was used with softmax function and skip layer connections from input to output. Maximum number of iterations was set to 100, and the maximum number of allowed weights was 1000000. The stopping fit criterion was set at 0.0000001 (indicating an essentially perfect fit) and the decay rate was set at 0.05. The classifier was trained with a 500-fold leave-one-out scheme. On each of 500 runs, 7 non-neglect and 7 neglect patients were randomly selected to train the model. 1 neglect and 1 of the 3 remaining non-neglect patients were reserved for cross-validation.

3. Results

3.1. Resting state functional connectivity

Group-averaged FDR-corrected functional connectivity results for the MN, VAN, and DAN are shown in Fig. 2. Averaged connectivity values were used in subsequent analyses.

3.2. General linear model analysis

3.2.1. Multivariate analysis of variance (MANOVA)—It was hypothesized that spatial neglect would have a significant effect on functional connectivity, such that connectivity would be reduced in the neglect compared to non-neglect group, even when controlling for lesion size and time since stroke. We were particularly interested in examining interhemispheric and intrahemispheric DAN connectivity, based on prior findings (Baldassarre et al., 2014, 2016). The MANOVA revealed a significant effect of spatial neglect on the interhemispheric connectivity within VAN ($F(1, 14) = 10.65$, $p < 0.005$), as well as a significant effect on bilateral VAN and left primary motor area (lM1) connectivity ($F(1, 14) = 6.28$, $p < 0.05$). Lastly, there was an effect of spatial neglect on VAN connectivity with the left Frontal Eye Field (lFEF) ($F(1, 14) = 7.26$, $p < 0.05$). Consistent with our hypothesis that spatial neglect adversely affects spatial- motor and attention network interaction, in all of these comparisons, connectivity was lower in the spatial neglect group. See Table 2 for means and standard deviations.

3.2.2. Regression with continuous behavioral inattention test-conventional subtest (BIT-c) score—Previous research found a positive relationship between visual attention deficits and internetwork MN, DAN, and VAN connectivity in each hemisphere, and a negative relationship with interhemispheric intranetwork connectivity (Baldassarre et al., 2014). In our data, none of the regression models in the spatial neglect group reached significance. In the non-neglect patients, contrary to the observed trends in the spatial neglect group, there was a significant relationship between the BIT-c score and functional connectivity measures, where worse vi- suospatial function was linked to higher internetwork connectivity, similarly to Baldassarre et al. (2014). Specifically, for both VAN to MN connectivity ($F(1, 9) = 12.77$, $p < 0.05$, FDR corrected for 12 comparisons) and VAN to DAN connectivity ($F(1, 9) = 18.51$, $p < 0.05$, FDR corrected), higher inter-network connectivity was predicted by lower BIT score (VAN to MN: $b_1 = -0.031$, $p < 0.01$; VAN to DAN: $b_1 = -0.03$, $p < 0.01$). Increased connectivity among resting state networks was previously explained by the loss of network differentiation corresponding to increased visual attention deficit (Baldassarre et al., 2014). However, unlike the previously reported findings, in our analysis this result was only observed in the non-neglect group. In this group, BIT-c score was also a significant predictor of interhemispheric VAN connectivity ($F(1, 9) = 11.10$, $p < 0.05$ FDR corrected), such that higher BIT-c was associated with lower connectivity ($b_1 = -0.03$, $p < 0.05$) (Fig. 3).

When both groups are considered together, BIT-c has a positive association with VAN, DAN, and MN interhemispheric connectivity. However, only VAN result survives FDR correction, with the others marginal ($p = 0.054$ and $p = 0.051$ for DAN and MN, respectively).

As illustrated by these results, the relationships between the BIT-c and functional connectivity are complex. We sought to determine if the association of attention and motor network co-activation has predictive validity for assigning patients to neglect positive and neglect negative groups. To this end, we validated our findings using hierarchical clustering (Murtagh & Legendre, 2014) and a neural network classifier.

3.3. Hierarchical cluster analysis

We explored the clustering solutions using both disability-relevant paper and pencil testing (BIT-c) and actual functional task performance (CBS via KF-NAP) to define spatial neglect, in order to maximize the external validity of our findings. Fig. 4A shows data clustering with participants labeled (post hoc) using their BIT-c score and spatial neglect classification. Fig. 4B shows the same clustering solution labeled with participants KF-NAP scores and neglect classification. At dendrogram height of 3, this method yields a 2 cluster solution, with the majority of neglect participants in one cluster and the majority of non-neglect participants in the other cluster. BIT-c seems to have a slightly better correspondence with the connectivity-based clustering than the KF-NAP. Thus, functional connectivity profiles of these participants naturally fall into two clusters based on the presence or absence of disability-relevant spatial neglect. Our connectivity-based method represent an improvement over rates of spatial neglect identification in clinical settings. For example, Edwards *et al.* reported that clinicians may fail to identify spatial neglect in as many as 61% of stroke patients during routine care (Edwards et al., 2006).

3.4. Classifier analysis

We explored the specificity and sensitivity of spatial neglect classification by classifier analysis, using disability-relevant paper and pencil testing (BIT-c) to define spatial neglect. The confusion matrix for 500 runs of the classifier analysis is shown in Table 3. The overall model proportion correct for the training set was 0.83 (or 83%), and for the cross-validation set was 0.79 (or 79%). The sensitivity of the model at cross-validation was 0.85, where sensitivity is defined as the proportion of actual positive cases correctly identified. The specificity was 0.72. Specificity was defined as the proportion of those without spatial neglect, who were identified as non-neglect by the classifier. Further-more, positive predictive value, defined as the proportion of cases identified as neglect that truly had neglect, was 0.75. Negative predictive value, defined as the proportion of cases identified as non-neglect that truly didn't have neglect, was 0.83. Thus, the neural network results provide an unbiased validated evidence linking functional connectivity in the MN, VAN, and DAN, with functionally-relevant spatial neglect.

4. Discussion

In this study, we establish that patients with spatial neglect, who were identified based on an externally-valid and disability-relevant assessment (the Behavioral Inattention Test-conventional (BIT-c; Halligan et al., 1991), demonstrate distinct neurophysiological and behavioral patterns of spatial-motor connectivity compared to controls. Our data confirm and extend the association of spatial neglect with abnormal interhemispheric functional connectivity of attention networks, reported previously in patients whose spatial deficits were defined by visual-spatial abnormalities without direct relationship to disability (Baldassarre et al., 2016). In other past studies, interhemi- spheric connectivity of the dorsal attention network was decreased in people with visual-spatial deficits (similarly-defined spatial neglect without functional predictive validity), as compared with controls. In our data, altered interhemispheric attention network connectivity was specific to the ventral, rather than the dorsal attention network, as previously reported (Baldassarre et al., 2016).

Further, we confirmed in *disability-relevant spatial neglect* a previous report that internetwork functional connectivity involving attention and motor systems is altered by spatial neglect (Baldassarre et al., 2014). In our data, however, *disability-relevant spatial neglect* was associated with decreased connectivity between bilateral ventral attention network and left primary motor area (lM1), as compared with patients who did not meet criteria for spatial neglect.

Our investigation includes a small sample size, which likely explains why the linear regression models in the neglect group did not reach significance. However, the strong finding of decreased interhemispheric VAN and internetwork VAN to MN and VAN to DAN connectivity in the spatial neglect group was ascertained using a MANOVA analysis. It is also possible, however, that previously-published changes in functional connectivity associated with spatial neglect are more relevant in people who have spatial or cognitive deficits, but do not meet criteria for disability-relevant spatial neglect. In our data, a linear relationship between spatial neglect scores and interhemispheric attention network connectivity, as well as a relationship between attention and motor inter-network connectivity, was observed only in patients who did not meet criteria for disability-relevant spatial neglect. It is possible that some of these people, however, had abnormal attention. They might have been classified as having spatial neglect as defined in previous functional connectivity studies with relatively difficult laboratory tasks (Baldassarre et al., 2014, 2016). We also observed a linear relationship between functional connectivity and the BIT-c, such that increased in- terhemispheric and intranetwork connectivity was associated with worse spatial neglect scores, in our group of right-stroke participants without spatial neglect. This is consistent with loss of network differentiation as described in Baldassarre et al. (2014).

Another possible explanation for increased interhemispheric and intranetwork connectivity in patients with attention deficits, but without disability-relevant spatial neglect, was that they may have had another co-morbid cognitive condition affecting brain network interaction (Boukrina & Barrett, 2017). For example, in a previous study of patients with delirium, (Choi et al., 2012) functional connectivity was increased in the “default mode” network and in a number of brain areas such as the basal forebrain and the thalamus, which may affect the level of activity in brain attention networks. Choi and colleagues did not explicitly study changes in attention and motor network interhemi- spheric and intrahemispheric internetwork connectivity. Therefore, we do not know whether the increases in attention-motor network connectivity observed in our study were also present in the delirium patients they studied. Future studies should carefully distinguish connectivity changes associated with different attentional disorders such as visuospatial dysfunction, versus delirium, versus *disability-relevant spatial neglect,* in order to clarify these issues.

We wished to ensure we included spatial neglect patients with large brain lesions and significant levels of daily life disability in our functional connectivity study, to determine whether these methods can be used to predict issues relevant to the impact of stroke on public health and the social cost of stroke. In previous studies (Baldassarre et al., 2014, 2016), many patients with large lesions affecting each functional connectivity ROI or its destination voxels were excluded. Indeed, the upper limit of lesion volume in these studies was at 90 cm^3, less than half the largest lesion volume in our study. Because we used a simplified approach, examining only 3 brain networks (as compared with 7–13 resting-state functional brain networks used in Baldassarre et al., 2014, 2016; Hacker, Laumann, Szrama, Baldassarre, & Snyder, 2013; Siegel et al., 2016) we were able to define networks based on 6 seed regions of interest in bilateral primary motor cortex, frontal eye field, and ventral frontal cortex. Although in some participants, part of a right brain region of interest was lesioned, we were able to study connectivity in all participants enrolled in the study and include all of the participants in the connectivity analysis. Thus, our study demonstrates that functional connectivity can be applied to examine typical stroke samples, and may be applicable to multi-site, spatial neglect clinical trials. Because it may be more potentially applicable to disabled patients with larger brain lesions, this method may eventually also be useful in applying functional connectivity for evaluation during clinical care.

We used a novel, machine-learning approach to classify patients as having *disability-relevant spatial neglect* based on the connectivity data collected by our simplified protocol, alone. In Table 3, the reader can see the outstanding performance of the model. Sensitivity of the model at cross-validation was 0.85, with specificity of 0.72. Furthermore, positive predictive value, defined as the proportion of cases identified as neglect that truly had neglect, was 0.75. Negative predictive value, defined as the proportion of cases identified as non-neglect that truly didn’t have neglect, was 0.83. Following analysis of functional connectivity measures, by validation with supervised and unsupervised learning algorithms, allowed us to take an important deductive step toward validated disease prediction.

24–82% of patients with spatial neglect are not identified during routine stroke care (Chen, McKenna, Kutlik, & Frisina, 2013; Edwards et al., 2006). Lesion locations associated with spatial neglect are highly variable (Baldassarre et al., 2014), and in rural and other underserved areas, trained clinicians are not available who can reliably identify spatial neglect by disability-relevant (Azouvi et al., 1996) or functional performance-based criteria (Chen et al., 2012). These results suggest that brain network functional connectivity analysis may yield physiologic signatures or biomarkers for the diagnosis of functionally-relevant spatial neglect. Using our simplified protocol may lead to a method of automated classification that is substantially superior to routine clinician assessment for spatial neglect diagnosis.

The relationship between attention and motor networks identified in our study confirms that identified in prior studies. Because spatial neglect is associated with maladaptive functional movements, this evidence of a physiologic relationship between spatial and motor function suggests that broader application of spatial retraining could improve safety and mobility after stroke. When patients with spatial neglect move the contralesional side of the body poorly, it is often unclear whether this is the result of true paralysis, or poor motor effort and spatial Aiming neglect. Automated, resting-state functional magnetic resonance imaging might be used in the future to assess the interaction of attention and motor systems, and clarify which disorder is causing poor movement. Then, patients with spatial neglect can be directed to targeted spatial retraining to improve function (Champod, Frank, & Eskes, 2016; Yang, Zhou, Chung, Li-Tsang, & Fong, 2013).

5. Summary

We evaluated functional connectivity among the motor, ventral and dorsal attention networks in 8 participants with post-stroke spatial neglect, and 10 participants with right-brain stroke but without *disability-relevant spatial neglect.* Decreased interhemispheric connectivity in the ventral attention network and decreased internetwork connectivity between the ventral attention and the motor network were found in patients with spatial neglect relative to the stroke control group. The motor and attention connectivity-based group assignment was validated using hierarchical clustering and neural network classification. These results are consistent with spatial neglect models in animals, and confirm and extend previous patient work to include stroke survivors with large lesions and functionally-disabling spatial neglect.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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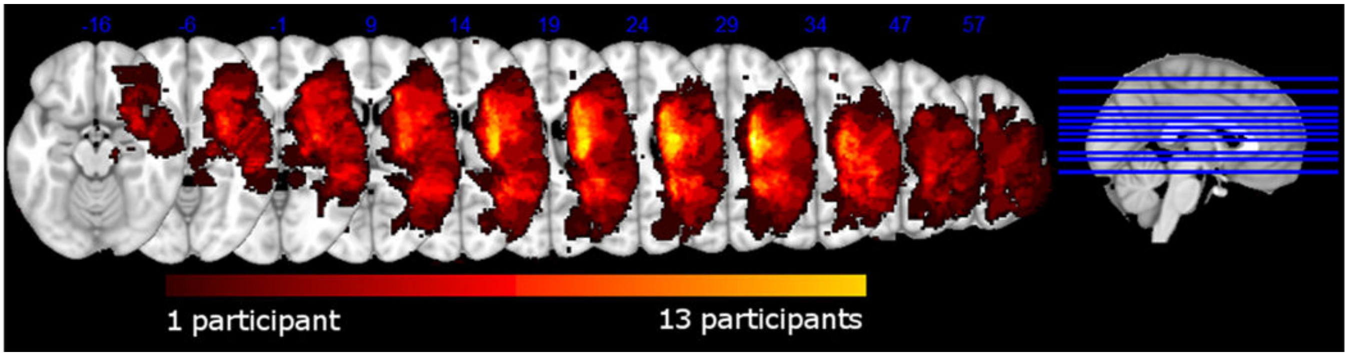

Fig. 1.

Group lesion coverage map for all patients in the study (N=18). Hot color represents areas of stroke lesion overlap, with maximal overlap occurring in 13 participants. Right brain is on the right side of image. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

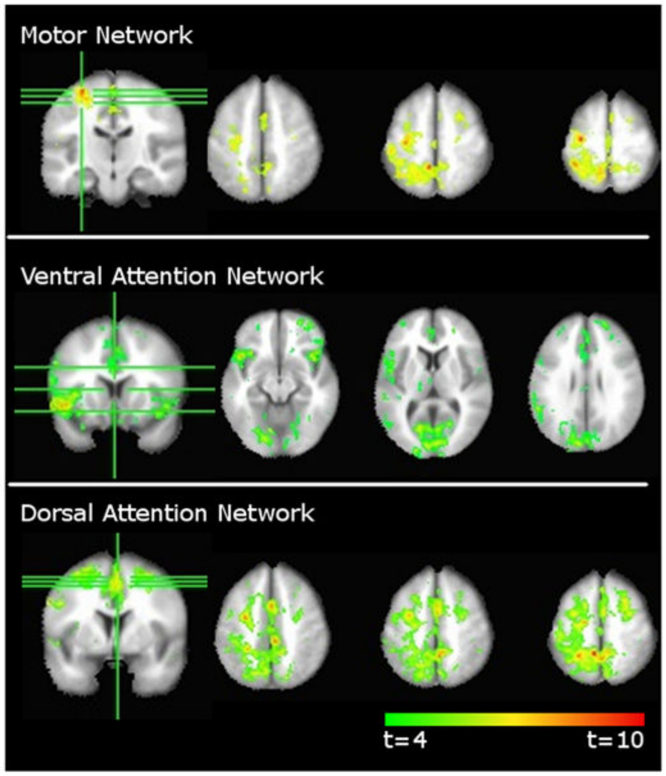

Fig. 2.
Group average of functional connectivity FDR-corrected at $p < 0.00005$. Right brain is on the right side of image.

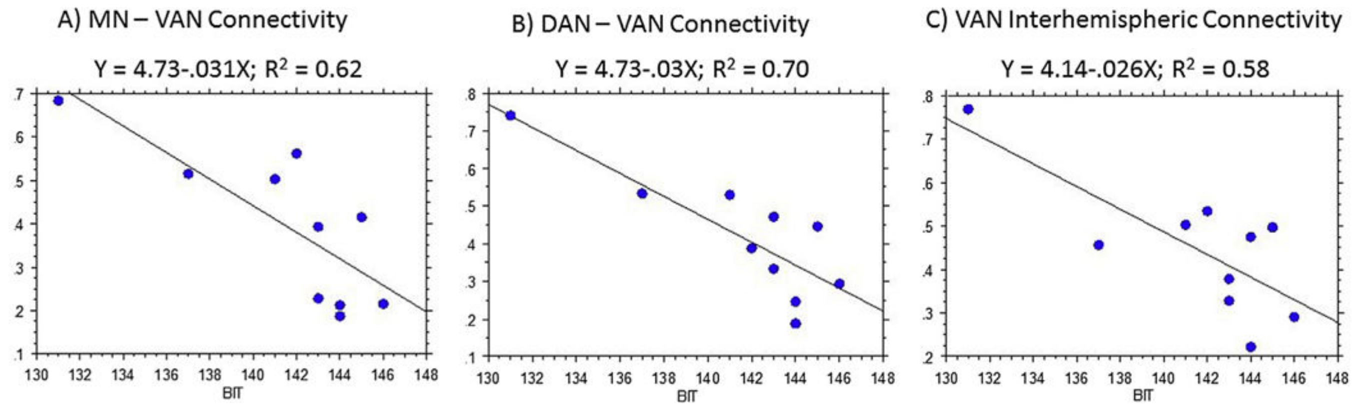

Fig. 3.

Regression plots showing significant relationship between BIT-c score and functional connectivity in the non-neglect group.

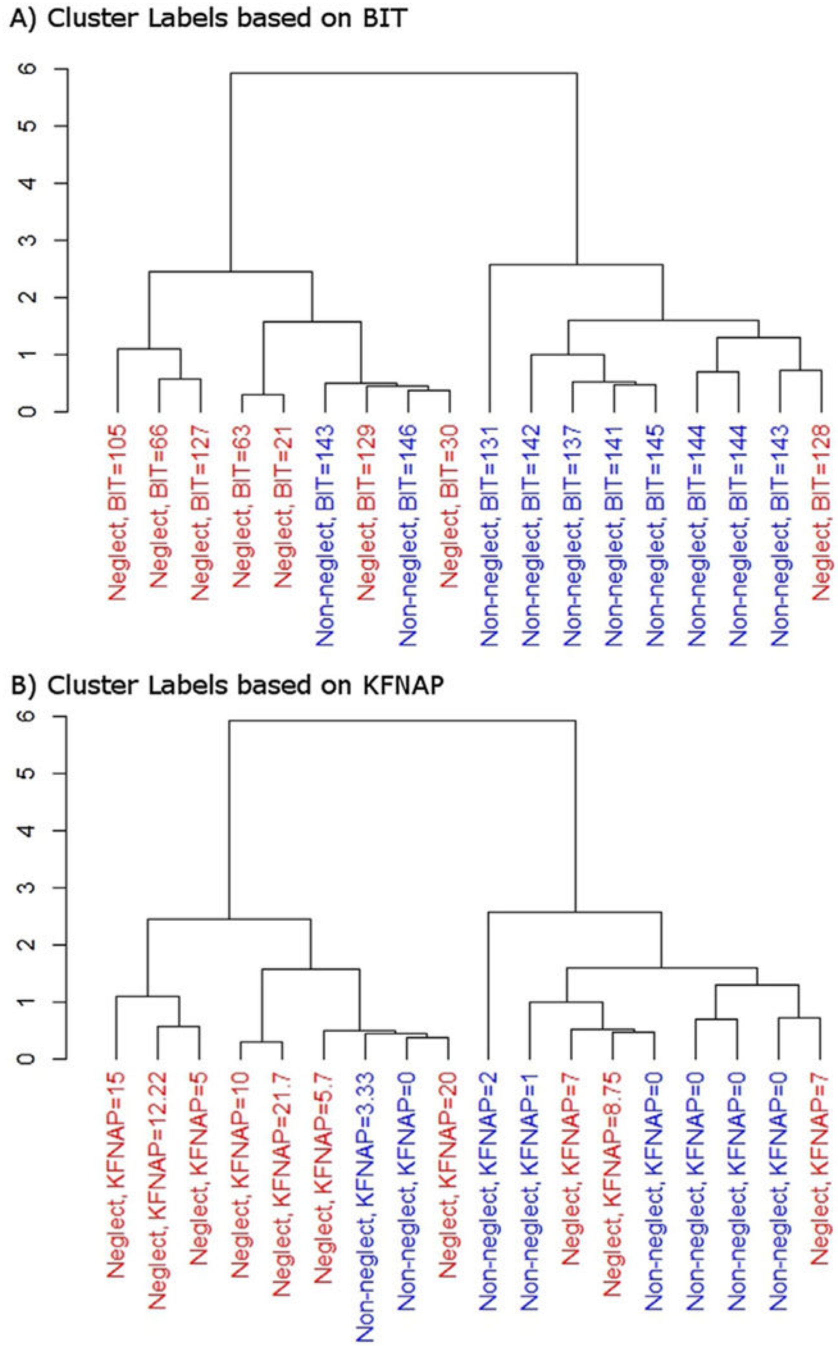

Fig. 4.

Hierarchical clustering of intra- and inter network functional connectivity in the motor, dorsal, and ventral attention networks labeled with each participant's spatial neglect status as defined by the behavioral inattention test-conventional subtest (BIT-c) score and by the Kessler Foundation Neglect Assessment Process (KF-NAP).

Table 1

Participant demographics.

Measure	With spatial neglect (based on BIT-c score) *Mean (SD), range* N = 8	Without spatial neglect *Mean (SD), range* N = 10	Total *Mean (SD), range* N = 18
Age (years)	58.0 (15.50), 30–73	55.8 (10.96), 36–70	56.8 (12.80), 30–73
Lesion Size (~cm3)	90.9 (72.52), 11.70–217.49	32.0 (30.68), 0.56–88.62	58.2 (59.76), 0.56–217.49
Behavioral Inattention Test-conventional (Halligan et al., 1991)	83.6 (44.56), 21–129	141.6 (4.48), 131–146	115.8 (41.32), 21 −146
Catherine Bergego Scale via the Kessler Foundation Neglect Assessment Process (Chen et al., 2015)	11.8 (6.76), 3.33–21.70	2.4 (3.38), 0–8.8	6.6 (6.91), 0–21.70

Table 2

Means and standard deviations of connectivity measures (correlation).

Connectivity	Mean	Standard Deviation	P-value
VAN			0.003
Neglect	0.14	0.14	
Non-neglect	0.45	0.15	
VAN and lM1			0.025
Neglect	0.08	0.15	
Non-neglect	0.32	0.21	
VAN and lFEF			0.017
Neglect	0.08	0.17	
Non-neglect	0.35	0.21	

Table 3

Neural network classifier confusion matrix.

Neural network classifier						
Training	Confusion matrix		Predicted			
			Neglect	Non-neglect		
	Actual	Neglect	0.87	0.13	Sensitivity (recall)	0.87
		Non-neglect	0.21	0.77	Specificity	0.77
			Positive predictive value (precision)	Negative predictive value	Accuracy	0.83
			0.80	0.85		
Cross-validation	Confusion matrix		Predicted			
			Neglect	Non-neglect		
	Actual	Neglect	0.85	0.15	Sensitivity (recall)	0.85
		Non-neglect	0.28	0.72	Specificity	0.72
			Positive predictive value (precision)	Negative predictive value	Accuracy	0.79
			0.75	0.83		
			95% CI: 0.82–0.89	95% CI: 0.68–0.76		