Title
Lateralized Resting-State Functional Brain Network Organization Changes in Heart Failure.

Permalink
https://escholarship.org/uc/item/93m2778c

Journal
PloS one, 11(5)

ISSN
1932-6203

Authors
Park, Bumhee
Roy, Bhaswati
Woo, Mary A
et al.

Publication Date
2016

DOI
10.1371/journal.pone.0155894

Peer reviewed
Lateralized Resting-State Functional Brain Network Organization Changes in Heart Failure

Bumhee Park†, Bhaswati Roy‡, Mary A. Woo‡, Jose A. Palomares¹, Gregg C. Fonarow³, Ronald M. Harper⁴,⁵, Rajesh Kumar¹,⁴,⁶,⁷*

¹ Department of Anesthesiology, University of California Los Angeles, Los Angeles, California, United States of America, ² UCLA School of Nursing, University of California Los Angeles, Los Angeles, California, United States of America, ³ Division of Cardiology, University of California Los Angeles, Los Angeles, California, United States of America, ⁴ Brain Research Institute, University of California Los Angeles, Los Angeles, California, United States of America, ⁵ Department of Neurobiology, University of California Los Angeles, Los Angeles, California, United States of America, ⁶ Department of Radiological Sciences, University of California Los Angeles, Los Angeles, California, United States of America, ⁷ Department of Bioengineering, University of California Los Angeles, Los Angeles, California, United States of America

† Current address: Department of Statistics, Hankuk University of Foreign Studies, Yongin, Republic of Korea
* rkumar@mednet.ucla.edu

Abstract

Heart failure (HF) patients show brain injury in autonomic, affective, and cognitive sites, which can change resting-state functional connectivity (FC), potentially altering overall functional brain network organization. However, the status of such connectivity or functional organization is unknown in HF. Determination of that status was the aim here, and we examined region-to-region FC and brain network topological properties across the whole-brain in 27 HF patients compared to 53 controls with resting-state functional MRI procedures. Decreased FC in HF appeared between the caudate and cerebellar regions, olfactory and cerebellar sites, vermis and medial frontal regions, and precentral gyri and cerebellar areas. However, increased FC emerged between the middle frontal gyrus and sensorimotor areas, superior parietal gyrus and orbito/medial frontal regions, inferior temporal gyrus and lingual gyrus/cerebellar lobe/pallidum, fusiform gyrus and superior orbitofrontal gyrus and cerebellar sites, and within vermis and cerebellar areas; these connections were largely in the right hemisphere (p<0.005; 10,000 permutations). The topology of functional integration and specialized characteristics in HF are significantly changed in regions showing altered FC, an outcome which would interfere with brain network organization (p<0.05; 10,000 permutations). Brain dysfunction in HF extends to resting conditions, and autonomic, cognitive, and affective deficits may stem from altered FC and brain network organization that may contribute to higher morbidity and mortality in the condition. Our findings likely result from the prominent axonal and nuclear structural changes reported earlier in HF; protecting neural tissue may improve FC integrity, and thus, increase quality of life and reduce morbidity and mortality.
Introduction

Heart failure (HF) patients show multiple autonomic, sensorimotor, mood, and cognitive deficits [1–4], which may originate from hypoxia/ischemia-induced brain injury by low cardiac output and sleep-disordered breathing, subsequent to cerebral hypo-perfusion in the condition [5–7]. Short-term memory loss is one of the most common cognitive changes reported in HF, with an incidence of ranging from 23–80% of HF cases (a risk of nearly twice that of healthy/non-HF patients) [8]. Also, executive decision making function is another serious cognitive deficit, affecting ~24% HF patients [9]. Persons with short-term memory loss and executive function deficit have impaired ability to learn and carry out important self-management strategies, such as to accurately and appropriately follow dietary and medication regimens, recognize symptoms associated with deteriorating health, and when to communicate with their health care provider [10, 11]. With the loss of memory and ability to learn how to self-manage their HF and decide upon needed communication with health care provider, there is increased risk for HF exacerbations and associated increased morbidity and mortality in this serious medical condition [1, 10, 11]. Similarly, high incidence of mood issues, including depression (40–60%) and anxiety (up to 45%) [2, 12] in HF patients may interfere with day-to-day self-management activity, and contribute to increased morbidity and mortality.

Brain structural injury appears in multiple brain regions serving autonomic, sensorimotor, mood, and cognitive functions based on various magnetic resonance imaging (MRI) procedures, including high-resolution T1-weighted imaging, T2-relaxometry, and diffusion tensor imaging (DTI) [13–16]. The structural impairments lead to aberrant functional MRI responses to autonomic challenges, including the Valsalva maneuver and cold pressor stimuli [3, 4, 17], and may also alter overall spontaneous functional organization, labeled “resting-state functional connectivity” (FC). It is reasonable to assume that impaired resting-state functional organization contributes to momentary neuropsychologic and physiologic pathology in HF, and may exacerbate the potential for further injury. However, whole-brain structural interactions during resting states (termed connection “weights” among brain regions) and coordination of these interactions (i.e., brain network organization) remain unclear in HF.

Resting-state functional MRI (rs-fMRI) procedures have been used to investigate region-to-region FC, a term which refers to temporal statistical dependency between neuronal activities of anatomically-distinct brain regions [18]. The procedure identifies synchronized spontaneous low-frequency (<0.1 Hz) fluctuation of blood-oxygen-level-dependent (BOLD) signals across the brain in the resting-state [19–21], which appear as consistent patterns across healthy subjects [22–25]. Resting-state FC procedures have been applied widely in various functional brain network studies, ranging from psychiatric to neurological conditions [26], and as well as in evaluation of human brain functions [27–29]. Since rs-fMRI FC procedures are used to discriminate healthy controls from patients (e.g., with stroke) [30], FC can be a potential biomarker and may be useful in assessing interactions of functional brain networks and coordination of these interactions in HF population.

Network-level approaches, based on graph theory, can describe the organizational properties of functional brain networks [31, 32]. A brain network can be modeled graphically, often called a “brain graph”, which consists of a set of nodes (brain regions) and edges (connectivity between nodes) [31, 33, 34]. Network-level approaches suggest that human brain networks are organized into modular systems, which are characterized by efficient integration of segregated brain regions through short paths, with low wiring costs, consisting of a few densely-connected core regions in the whole-brain [31, 32, 35]. These organizational brain attributes have been found in both anatomical, using DTI or cortical thickness assessments [36–40], and functional networks, using MEG, EEG, or fMRI [41–45]. It has been suggested that cognitive processing is
based on high global efficiency in brain networks to efficiently integrate neural information across whole-brain sites [34], where some hubs (e.g., brain regions concentrated by a large number of connections with the rest of whole-brain) play a pivotal role showing high cost for conveying neural information and are especially vulnerable to aberrant disease conditions [46]. Various disease conditions, including Schizophrenia, Alzheimer’s disease, and Parkinson’s disease [46], show that pathological brain areas are significantly concentrated in such hub sites playing critical role in normal functional brain network, although cortical hubs are differently lesioned in each disorder. Thus, network-level approaches may also yield important macroscopic or topological alterations on functional brain network in HF patients as well.

Our aim was to investigate functional interactions and organizational properties across the whole-brain in HF patients over age- and gender-comparable controls using FC and basic network-level approaches. We hypothesized that HF patients would show intrinsically-abnormal brain FC and functional coordination among the regions serving multiple autonomic, sensorimotor, mood, and cognitive roles in HF.

**Materials and Methods**

**Subjects**

We investigated 27 hemodynamically-optimized (drug dosages were titrated to reach targeted hemodynamic goals) HF patients and 53 age- and gender-comparable healthy controls. Demographic and clinical data of all HF patients and controls are summarized in Table 1. All HF patients were recruited from the Ahmanson-University of California at Los Angeles (UCLA) Cardiomyopathy Center. The diagnosis of HF was based on national diagnostic criteria [47], and all subjects included in this study were with NYHA Functional Class II at the time of MRI [48]. All HF patients enrolled here were between 30–66 years of age. Lower age was chosen to minimize developmental process and higher age was chosen to reduce aging effect. All HF patients were without any history of drug abuse, valvular congenital heart defects, pregnancy induced cardiomyopathy, no previous history of stroke or carotid vascular disease, and head injury. All HF patients were treated with guideline-directed medical therapy, including angiotensin receptor blockers or angiotensin-converting enzyme inhibitors, beta blockers, and diuretics, and were stabilized for hemodynamics and body-weight for at least six months prior to participation in MRI studies.

Control subjects were recruited through advertisements at the UCLA campus and Los Angeles area. All control subjects were in good health, without any clinical history of cardiovascular, stroke, respiratory, neurological, or psychiatric disorders that may introduce brain changes.

Both HF patients and controls were excluded from the study if they were claustrophobic, carrying non-removable metal, such as embolic coils, pacemakers/implantable cardioverter-defibrillators, stents, or with body weight more than 125 kg (the last, a scanner limitation). All subjects gave written and informed consent before data acquisition and study protocol was approved by the Institutional Review Board at the UCLA.

**Mood and sleep examination**

Beck Depression Inventory II (BDI-II) was used to assess depressive symptoms, and Beck Anxiety Inventory (BAI) was used to examine anxiety symptoms in HF patients and controls [49, 50]. Both BDI-II and BAI are self-administered questionnaires (21 questions; each score ranged from 0–3) with total scores ranging from 0–63, based on mood or anxiety symptoms.
Sleep quality and daytime sleepiness were evaluated in HF patients and controls. We used the Pittsburgh Sleep Quality Index (PSQI) [51] and Epworth Sleepiness Scale (ESS) [52] to examine sleep quality and daytime sleepiness, respectively.

**Cognition assessment**

The Montreal Cognitive Assessment (MoCA) test was used for cognitive assessment. The test contains various cognitive domains, including attention, executive functions, memory, language, visuo-constructional skills, conceptual thinking, calculations, and orientation [53].

**Magnetic resonance imaging**

Brain imaging of HF patients and controls was performed using a 3.0-Tesla MRI scanner (Siemens, Magnetom Tim-Trio, Erlangen, Germany). Foam pads were used on either side of the head to reduce head motion-related artifacts during scanning. Rs-fMRI data were acquired with an echo planar imaging based BOLD sequence in the axial plan [repetition time (TR) = 2000 ms; echo time (TE) = 30 ms; flip angle (FA) = 90°; field-of-view (FOV) = 230×230 mm²; matrix size = 64×64; voxel size = 3.59×3.59×4.5 mm³; volumes = 59], while participants lay resting with their heads in the scanner.

### Table 1. Demographic, clinical, and sleep variables of HF and control subjects.

| Variables | HF (n = 27) | Controls (n = 53) | P-value |
|-----------|-------------|-------------------|---------|
| Age range (y) | 40–66 | 40–66 | – |
| Age (mean ± SD, yrs) | 55.3 ± 7.9 | 52.7 ± 6.2 | 0.11 |
| Sex (Male:Female) | 20:7 | 36:17 | 0.57 |
| BMI (mean ± SD, kg/m²) | 27.9 ± 5.5 | 25.4 ± 3.5 | 0.01 |
| Handedness | 2 Left; 24 Right; 1 Ambidextrous | 10 Left; 42 Right; 1 Ambidextrous | – |
| Ethnicity | 1 Asian; 17 White; 6 Hispanic; 6 African-American; 1 Armenian | 14 Asian; 25 White; 8 Hispanic; 3 African-American; 1 White-Asian; 1 Hispanic-White; 1 El Salvador-Hispanic | – |
| PSQI (mean ± SD) | 7.2 ± 3.9 | 4.0 ± 2.6 | <0.001 |
| ESS (mean ± SD) | 5.4 ± 3.2 (n = 26) | 8.0 ± 4.2 | 0.0027 |
| BDI-II (mean ± SD) | 10.3 ± 7.1 | 3.9 ± 4.1 | <0.001 |
| BAI (mean ± SD) | 9.5 ± 8.0 | 3.7 ± 4.7 | <0.001 |
| LVEF (mean ± SD) | 28.0 ± 9.2 | – | – |
| Global MoCA scores (mean ± SD) | 24.9 ± 3.4 (n = 10) | 27.7 ± 1.9 (n = 16) | 0.01 |
| MoCA: Visuospatial (mean ± SD) | 3.3 ± 1.4 (n = 10) | 4.4 ± 0.6 (n = 16) | 0.04 |
| MoCA: Naming (mean ± SD) | 3.0 ± 0.0 (n = 10) | 2.8 ± 0.6 (n = 16) | 0.10 |
| MoCA: Attention (mean ± SD) | 5.5 ± 0.8 (n = 10) | 5.6 ± 0.6 (n = 16) | 0.83 |
| MoCA: Language (mean ± SD) | 2.2 ± 0.8 (n = 10) | 2.7 ± 0.8 (n = 16) | 0.14 |
| MoCA: Abstraction (mean ± SD) | 2.0 ± 0.0 (n = 10) | 2.0 ± 0.0 (n = 16) | 1.0 |
| MoCA: Delayed recall (mean ± SD) | 2.9 ± 1.8 (n = 10) | 4.3 ± 0.9 (n = 16) | 0.04 |
| MoCA: Orientation (mean ± SD) | 6.0 ± 0.0 (n = 10) | 6.0 ± 0.0 (n = 16) | 1.0 |

BMI, Body mass index; ESS, Epworth sleepiness scale; PSQI, Pittsburgh sleep quality index; BDI-II, Beck depression inventory II; BAI, Beck anxiety inventory; LVEF, Left ventricular ejection fraction; MoCA, Montreal Cognitive Assessment; SD, Standard deviation.

doi:10.1371/journal.pone.0155894.t001
eyes open, without focusing on specific thoughts, and no sleeping during about 2 minutes.
High resolution T1-weighted images were collected from each subject using a magnetization prepared rapid acquisition gradient-echo pulse sequence (TR = 2200 ms; TE = 2.2, 2.34 ms; FA = 9°; FOV = 230×230 mm²; matrix size = 256×256, 320×320; voxel size = 0.9×0.9×1.0 mm³, 0.72×0.72×0.9 mm³). Proton-density (PD) and T2-weighted images were acquired in the axial plane, using a dual-echo turbo spin-echo pulse sequence (TR = 10,000 ms; TE1, 2 = 17, 134 ms; FA = 130°; matrix size = 256×256; FOV = 230×230 mm²; voxel size = 0.9×0.9×4.0 mm³).

Data preprocessing
We used the statistical parametric mapping (SPM8, Wellcome Department of Cognitive Neurology, London, UK) [54] and MRICroN software [55] for evaluation of images and rs-fMRI data preprocessing. High-resolution T1-weighted, PD-, and T2-weighted images of HF patients and controls were examined for any gross brain pathology, such as tumors, cysts, or major infarcts. Rs-fMRI data were also assessed for imaging or head motion-related artifacts before data processing. No subjects included in this study showed any serious visible brain pathology, head motion-related, or other imaging artifacts.

Resting-state fMRI data preprocessing steps included realignment of EPI brain volumes for removal of any potential head-motion, co-registration to T1-weighted images, and spatial normalization to a standard common space template using nonlinear transformation procedures. For rs-fMRI data analysis, we discarded the initial 3 brain volumes to avoid signal saturation issues, and used the remaining 56 volumes for remaining analysis. No spatial smoothing was performed on the rs-fMRI data to avoid inflation of local connectivity and clustering [56].

Construction and analysis of functional network
Individual whole-brain FC was determined from regional mean fMRI time series, extracted from 116 distinct regions, as defined by automated anatomical labeling [57], that consists of 90 cerebral brain regions (45 sites in each hemisphere) and 26 cerebellar areas (9 regions in each hemisphere and 8 vermis sites), as described in Table 2. We applied the canonical signal processing procedures for calculating the rs-FC for each regional mean fMRI time series [58]. Each time series was band-pass filtered (0.009–0.08 Hz), and effects of six rigid motions, their first derivatives, and global signal changes in white matter, cerebrospinal fluid, and whole-brain were removed by regression. The first derivatives of the motion parameters were added in the statistical model to minimize signal changes from head-motion [59], which is often an issue in any rs-FC study [59–61]. We defined FC (edge) as an inter-regional correlation map among 116 preprocessed regional time series. We converted individual correlation maps into z-scored maps with Fisher’s r-to-z transformation to improve normality. We compared the z-scored maps edge-by-edge between HF patients and controls using analysis of covariance (ANCOVA), with age and gender included as covariates. We also examined relationships between each variable (BMI, LVEF, PSQI, ESS, BAI, or BDI-II) and functional connectivity. All rs-FC analyses were performed using MATLAB-based custom software.

Brain network analysis
Organizational characteristics on functional networks of HF patients and controls were assessed with graph-theoretical analyses [62], using the Brain Connectivity Toolbox (http://www.brain-connectivity-toolbox.net/). We consider brain networks as a graph, G = (N, E), which consists a set of nodes N (brain regions) and connections E (functional connectivity) [31]. Using a threshold of false discovery rate (FDR) < 0.05 [63], we constructed individual brain networks. We considered connected edge weights, if the values were statistically
significant, and otherwise set those values to zero and considered not connected. Brain networks were examined for network centrality (degree, strength, and betweenness), network segregation (clustering coefficient and local efficiency), and network integration (nodal efficiency and global efficiency) [31, 32, 62].

Nodal (or regional) degree is defined as the number of connections linking the node to rest of the networks [62], and a brain region showing larger degree values plays a functional core role to highly integrate the multiple specialized functions at different brain regions. Nodal strength, as the weighted degree, is defined as the sum of connection strengths linking the node to rest of the network, and serves as the total level of connection weight information in the node [62]. A larger strength value represents a region that exerts greater connection strength in the communication, and involves a high level of integration in whole-brain communication. Betweenness for a node is measured as the fractional shortest path between any other node pair in the network passing through the node [62]. A brain region showing a higher betweenness value implies that a large number of the shortest path lengths pass through the region, and

| Regions | Abbreviation | Regions | Abbreviation |
|---------|--------------|---------|--------------|
| Precentral gyrus | PrCG | Supramarginal gyrus | SMG |
| Superior frontal gyrus (dorsolateral part) | SFGdor | Angular gyrus | ANG |
| Orbitofrontal gyrus (superior part) | OFGsup | Precuneus | PRCU |
| Middle frontal gyrus | MFG | Paracentral lobule | PCL |
| Orbitofrontal gyrus (middle part) | OFGmid | Caudate | CAU |
| Inferior frontal gyrus (opercular part) | IFGop | Putamen | PUT |
| Inferior frontal gyrus (triangular part) | IFGtr | Pallidum | PAL |
| Orbitofrontal gyrus (inferior part) | OFGinf | Thalamus | THL |
| Rolandic operculum | ROL | Heschl gyrus | HES |
| Supplementary motor area | SMA | Superior temporal gyrus | STG |
| Olfactory cortex | OLF | Temporal pole (superior part) | TPsup |
| Superior frontal gyrus (medial part) | SFGmed | Middle temporal gyrus | MTG |
| Orbitofrontal gyrus (medial part) | OFGmed | Temporal pole (middle part) | TPmid |
| Rectus | REC | Inferior temporal gyrus | ITG |
| Insula | INS | Cerebellar crus I | CRcr-I |
| Anterior cingulate cortex | ACC | Cerebellar crus II | CRcr-II |
| Middle cingulate cortex | MCC | Cerebellum III | CR-III |
| Posterior cingulate cortex | PCC | Cerebellum IV-V | CR-IV |
| Hippocampus | HP | Cerebellum VI | CR-VI |
| Parahippocampal gyrus | PHG | Cerebellum VIIb | CR-VIIb |
| Amygdala | AMYG | Cerebellum VIII | CR-VIII |
| Calcarine | CAL | Cerebellum IX | CR-IX |
| Cuneus | CUN | Cerebellum X | CR-X |
| Lingual gyrus | LING | Vermis I-II | VM-I |
| Superior occipital gyrus | SOG | Vermis III | VM-III |
| Middle occipital gyrus | MOG | Vermis IV-V | VM-IV |
| Inferior occipital gyrus | IOG | Vermis VI | VM-VI |
| Fusiform gyrus | FFG | Vermis VII | VM-VII |
| Postcentral gyrus | PoCG | Vermis VIII | VM-VIII |
| Superior parietal gyrus | SPG | Vermis IX | VM-IX |
| Inferior parietal lobule | IPL | Vermis X | VM-X |

doi:10.1371/journal.pone.0155894.t002
that the region exerts a high influence in the network communication. The level of functional communication efficiency between any two brain regions can be assumed to be the inverse of the weighted shortest path length, which is the weight sum of connections that must be traversed to travel from one node to another [64]. Weighted nodal efficiency is expressed as the averaged inverse weighed shortest path length to the rest of the network, and global efficiency is defined as the average of all nodal efficiencies [64, 65]. Larger efficiency or shorter path lengths of a region might thus represent that the area communicates more efficiently with the rest of the brain. The level at which a network is organized into densely clustered nodes can be assessed using the clustering coefficient [35]. Weighted clustering coefficient for a region quantifies the number of actual connections existing among the region’s neighbors, proportional to the number of all their possible connections, and a brain region showing a higher weighted clustering coefficient value implies densely linked local structures among the neighboring sites. The segregation index, which is a weighted cluster coefficient, is considered as the weighted shortest path length within the neighbors [62].

Statistical analyses

The IBM Statistical Package for the Social Sciences (IBM SPSS, v 22, Armonk, NY) software was used to assess demographic, biophysical, and other clinical variables. Demographic, sleep, and other clinical variables were assessed by Chi-square and independent samples t-tests. A threshold value of $p < 0.05$ was considered statistical significance.

We examined FC and graph-theoretical measures between groups using the random permutation test in a nonparametric fashion ($p < 0.005$ for FC, $p < 0.05$ for graph-theoretical measures, 10,000 permutations) [66]. We created a null distribution of t-statistics for each measurement from analysis of covariance (ANCOVA; covariates, age and gender), using group labels randomly-shuffled 10,000 times, with assumption of no significant differences between HF patients and controls. We compared original t-statistic values from ANCOVA with the null distribution, and considered those values significant if they exceeded the distribution threshold. Also, relationships between each variable (BMI, LVEF, PSQI, ESS, BAI, or BDI-II) and FC were examined with partial correlation procedures, with age and gender as covariates (Correlation of BMI, LVEF, PSQI, ESS, BAI, or BDI-II with FC, S1 Fig).

Results

Demographic and clinical characteristics

HF patients did not differ in age ($p = 0.11$) or gender ($p = 0.57$) compared to controls (Table 1). However, BMI values in HF patients were significantly larger, compared to controls ($p = 0.014$). Other measurements, including the sleep scores (PSQI, $p < 0.001$; ESS, $p = 0.0027$), mood values (BDI-II, $p < 0.001$; BAI, $p < 0.001$), and cognitive scores (MoCA, $p = 0.01$) also showed significant differences between groups (Table 1).

Whole-brain FC

Significantly altered FC appeared in various brain sites across whole-brain areas in HF, compared to healthy controls ($p < 0.005$, 10,000 permutations), these sites are shown in Figs 1–3, and areas listed in Tables 3 and 4. Decreased FC in HF (Figs 1b and 2), emerged principally between the caudate and cerebellar regions, olfactory and cerebellar sites, vermis and medial frontal regions, and precentral gyri and cerebellar areas. However, increased FC in HF (Figs 1b and 3) appeared between the middle frontal gyrus and sensorimotor regions, superior parietal gyrus and orbito/medial frontal regions, inferior temporal gyrus and lingual gyrus/cerebellar
lobe/pallidum, fusiform gyrus and superior orbitofrontal gyrus and cerebellar sites, and within vermis and cerebellar areas, and these connections are largely lateralized to the right hemisphere. Associations between BMI, LVEF, PSQI, ESS, BAI, and BDI-II and functional connections weakly increased or decreased in HF with lower significant level of $P < 0.05$ ($r = 0.38$, correlation coefficient) (Correlation of BMI, LVEF, PSQI, ESS, BAI, or BDI-II with FC, S1 Fig).

**Decreased FC in HF.** Both the left and right precentral gyrus showed decreased FC in HF with regions in the right hemisphere, i.e., the right cerebellar lobe VIIb/VIII and fusiform gyrus connected with the left precentral gyrus and the right pallidum, fusiform gyrus, and inferior occipital gyrus connected with the right precentral gyrus. Connectivity between the left post-central gyrus and left cerebellar lobe VIII was also diminished in HF. The right paracentral lobe showed decreased connections with the bilateral cuneus, and the right olfactory with the
cerebellar regions, including the right crus I, right lobe VI, and vermis VI. The right rectus showed reduced FC with the left rectus and right Rolandic operculum, and with right middle and superior orbitofrontal gyri. The vermis X showed decreased FC with the bilateral medial superior frontal and right medial orbitofrontal gyri. The right caudate remarkably showed

Fig 2. Decreased FC in HF over control subjects. Significantly decreased FC appeared in multiple areas between brain sites in HF patients. Thicker edge lines represent more significant differences, with a scale of $-\log_{10}(P\text{-value})$ from a minimum value to 6, surviving a threshold of $p<0.005$ (10,000 permutations). Bigger nodal sphere size represents a larger number of significant edges. Bold yellow labels indicate sites with at least 3 functional connections. Brain sites with abbreviations are same as listed in Table 2.

doi:10.1371/journal.pone.0155894.g002
decreased FC with the cerebellar sites, including the right crus I, bilateral lobe VI, and vermis VI. However, the left caudate showed reduced FC with the left pallidum only. Also, decreased FC emerged between the cerebellar and posterior parietal regions, including the posterior cingulate cortex, precuneus, inferior parietal lobule, and supramarginal gyrus.

Fig 3. Increased FC in HF over control subjects. Significantly increased FC in areas between brain regions in HF patients. Thicker edge lines represent more significant differences, with a scale of $-\log_{10}(P\text{-value})$ from a minimum value to 6, surviving a threshold of $p<0.005$ (10,000 permutations). Larger nodal sphere size represents a bigger number of significant edges. Bold yellow labels indicate sites with at least 3 functional connections. Brain sites with abbreviations are same as listed in Table 2.

doi:10.1371/journal.pone.0155894.g003
Table 3. Significantly decreased FC between brain areas in patients with HF (P<0.005, 10,000 permutations).

| Regions | Regions | P-value | Regions | Regions | P-value |
|---------|---------|---------|---------|---------|---------|
| Right CAU | Right Crcr-I | 0.0021 | Right REC | Left REC | 0.0017 |
| Right CAU | Left CR-VI | 0.0002 | Right REC | Right ROL | 0.001 |
| Right CAU | Right CR-VI | 0.004 | VM-X | Left SFGmed | 0.0023 |
| Right CAU | VM-VI | 0.0008 | VM-X | Right SFGmed | 0.0038 |
| Left CAU | Left PAL | 0.003 | VM-X | Right OFGmed | 0.0034 |
| Right PUT | Left HP | 0.0014 | Left PRCU | Right CR-Iv | 0.0029 |
| Left PrCG | Right FFG | 0.0035 | Left PRCU | Left CR-X | 0.0024 |
| Left PrCG | Right CR-VIlb | 0.0004 | Left PCC | Right SMG | 0.0004 |
| Left PrCG | Right CR-VIII | 0.0031 | Left PCC | Right CR-XI | 0.0003 |
| Right PrCG | Right PAL | 0.0029 | Right IPL | VM-VII | 0.0037 |
| Right PrCG | Right FFG | 0.0008 | Right ANG | Left HES | 0.002 |
| Right PrCG | Right IOG | 0.0024 | Left SPG | Left CR-VI | 0.0039 |
| Left PoCG | Left CR-VIII | 0.0012 | Left ROL | Left Crcr-II | 0.0026 |
| Right PCL | Left CUN | 0.0007 | Right ROL | Right CR-VIlb | 0.0038 |
| Right PCL | Right CUN | 0.0038 | Right OFGmid | Right OFGsup | 0.0045 |
| Right OLF | Right Crcr-I | 0.0018 | Left IFGop | Right MOG | 0.004 |
| Right OLF | Right CR-VI | 0.0005 | Right SFGmed | Right Tpmid | 0.0024 |
| Right OLF | VM-VI | 0.0001 | Left SMA | Right STG | 0.0027 |

Brain sites with abbreviations are same as listed in Table 2.

doi:10.1371/journal.pone.0155894.t003

Table 4. Significantly increased FC between brain sites in patients with HF (P<0.005, 10,000 permutations).

| Regions | Regions | P-value | Regions | Regions | P-value |
|---------|---------|---------|---------|---------|---------|
| Right MFG | Right PrCG | 0.0044 | Left PRCU | Left SPG | 0.0004 |
| Right MFG | Left PoCG | 0.0015 | Right PRCU | Right MOG | 0.0024 |
| Right MFG | Right PoCG | 0.0033 | Right ROL | Right CAL | 0.0046 |
| Right MFG | Right PCL | 0.0036 | Right ROL | Left HES | 0.0043 |
| Right SPG | Right OFGmed | 0.0038 | Right MCC | Left SOG | 0.0049 |
| Right SPG | Left REC | 0.0049 | Left PCC | Right IOG | 0.0038 |
| Right SPG | Right REC | 0.0002 | Right AMYG | Left CR-X | 0.0037 |
| Right SPG | Left ACC | 0.0007 | Left AMYG | Left MTG | 0.0036 |
| Right FFG | Right OFGsup | 0.0029 | Right HP | VM-III | 0.0043 |
| Right FFG | VM-VI | 0.0004 | VM-III | Left THL | 0.0019 |
| Right FFG | Left CRcr-II | 0.0044 | Left CRcr-II | Right MOG | 0.0045 |
| Right FFG | VM-VII | 0.0033 | VM-I | Right SFGdor | 0.0006 |
| Right ITG | Right LING | 0.0048 | Right CR-VI | Left CR-III | 0.0028 |
| Right ITG | Left CR-VI | 0.0006 | Right CR-VI | VM-X | 0.0039 |
| Right PAL | Right ITG | 0.0026 | Left CR-IV | VM-VI | 0.0009 |
| Right PAL | Left MTG | 0.0045 | Left CR-IV | VM-VIII | 0.0027 |
| Left PAL | Right Tpmid | 0.004 | Left CR-IV | VM-X | 0.0005 |
| Right INS | Left Tpmid | 0.0022 | VM-IV | Left CR-VIII | 0.0032 |
| Right INS | Right CR-III | 0.0017 | VM-IV | VM-VI | 0.0022 |
| Left INS | Right CAL | 0.0017 | VM-VIII | Left CR-VI | 0.0025 |

Brain sites with abbreviations are same as listed in Table 2.

doi:10.1371/journal.pone.0155894.t004
**Increased FC in HF.** The right middle frontal gyrus showed increased FC with the bilateral postcentral gyri, right precentral gyrus, and right paracentral lobule. Several sites within cerebellar areas emerged with increased FC between the vermis VI and the vermis IV, and between left cerebellar lobe IV-VI and the vermis VIII-X. The right superior parietal gyrus showed increased FC with the bilateral rectus, right medial orbitofrontal gyrus, and left anterior cingulate cortex. The right insula showed increased FC with the left middle temporal pole and right cerebellar lobe III, while the left insula with the right calcarine. Connections between the right amygdala and left cerebellar lobe X, the left amygdala and the left middle temporal gyrus, the right hippocampus and vermis III, and the left thalamus and vermis III appeared with increased FC. In addition, the right fusiform gyrus showed enhanced FC with the right superior orbitofrontal gyrus, left cerebellar crus II, and vermis VI-VII. However, the right inferior temporal gyrus showed increased FC with the right lingual gyrus, left cerebellar lobe VI, and right pallidum.

**Topological measures**

Nodal topological measures in HF showed altered values in widespread brain regions (Fig 4, Table 5; p<0.05, 10,000 permutations). Network centrality measures in HF appeared with

---

Fig 4. Graph-theoretical measures in HF subjects. Significantly decreased (a) or increased (b) graph-theoretical measures in HF subjects (p<0.05, 10,000 permutations). Each circle represents significantly changed regional (or nodal) properties, with various color representing strength, degree, weighted clustering coefficient, betweenness centrality, and nodal efficiency, respectively. Brain sites with abbreviations are same as listed in Table 2.

doi:10.1371/journal.pone.0155894.g004
decreased betweenness centrality at the left para-hippocampal gyrus, left and right supramargi-
mal gyrus, and vermis VI, and decreased degree at the right thalamus. Increased betweenness
centrality emerged at the right medial orbitofrontal gyrus, right rectus, left olfactory, bilateral
middle temporal pole, left inferior occipital gyrus, and right cerebellar lobule X. However,
increased degree appeared at the left middle temporal pole, right angular gyrus, right inferior
occipital gyrus, and vermis III, and increased strength at the right angular gyrus and right infe-
rior occipital gyrus. HF subjects showed increased weighted clustering coefficient at the left
precentral gyrus, left Rolandic, right cerebellar lobule IV-V, and vermis VI, and increased
nodal efficiency at the left precentral, left Rolandic, left heschl, right angular gyrus, and cerebel-
lar lobule IV-V. Both weighted clustering coefficient and nodal efficiency did not show any site
with decreased value in HF. Also, global network properties, including global and local effi-
ciency, did not show any significant difference.

### Discussion

We examined whole-brain FC and their network organizational properties in HF patients com-
pared to controls using rs-fMRI procedures. A core question was how brain dysfunction in HF
condition affects individual functional interactions and coordination among sites across the
whole-brain. Our data suggest that HF patients have aberrant spontaneous functional connec-
tions in various brain areas, especially lateralized to the right hemisphere. These aberrant con-
nections are related to sensorimotor, autonomic, mood, and cognitive regulation, sites which
have been reported as having structural injury or being deficient in function when challenged
in previous HF studies. Moreover, functional interactions altered in HF contribute to aberrant
brain network organization in the condition.
Functional reorganization in autonomic, respiratory, and sensorimotor networks

Autonomic dysfunction, including increased sympathetic tone, aberrant heart rate, and blood pressure responses to cardiovascular challenges, is a core characteristic in HF [3, 4, 67, 68]. Damaged brain structures in HF include the insular, cingulate, orbitofrontal, hypothalamus, and cerebellar regions [13–16].

The right and left insular cortices exert influences on sympathetic and parasympathetic nervous system activity [69–71] and both receive visceral sensory input from, and project to, the hypothalamus, participating significantly in autonomic regulation [71]. In addition, the insular cortices play significant roles in pain mediation [72], and in dyspnea [73], both issues of concern in HF. The cingulate cortex, which receives axons from and projects to insular cortices, mediates both autonomic sympathetic and parasympathetic branches, and damage to this structure can impact cardiac regulation [3, 15, 74, 75]. The orbitofrontal cortex exerts prominent influences on somatomotor inhibition of autonomic responses, and coordination of behavioral responses during adaptation [76] and shows a substantial role in initiation of blood pressure responses [77]. The cerebellar cortices and vermis play autonomic and respiratory motor regulation [78, 79], and are one of the heavily damaged regions in HF [13–16], and also show altered autonomic responses to cardiovascular challenges [3, 4].

Over the regional FC changes, our findings show that the injury in these autonomic and respiratory control sites further leads to decreased functional interactions among these regions and/or with other cognitive control regions (e.g., the bilateral medial superior frontal gyri). Notably, such declines in FC are primarily localized in the right hemisphere, and the right olfactory and vermis X were sites to play key roles. The functional lateralization in HF may couple with lateralized tissue damage in the condition, which consistently appeared in the previous studies [13, 15, 16]. Increased functional interactions with the bilateral insula and increased within-cerebellar regions in HF may correspond to enhanced local plasticity of fibers, such that additional regions are recruited for the diverse functional compensatory processes. Such processes are necessary to protect against abnormalities that appear in HF, consequences of vulnerable regulation by exaggerated sympathetic outflow or metabolic stress [80].

Reorganization of FC in autonomic and respiratory systems in HF subjects may also underlie deficient sensorimotor processes, reflecting distorted sensory input from the upper airway, and contributing to the atonia in upper airway muscles during inspiratory efforts of obstructed breathing in HF. Here, distorted sensorimotor integration appeared as decreased FC largely involved in the bilateral precentral gyri, as well as in the right paracentral lobule and left postcentral gyrus. Moreover, these decreased connections are largely lateralized in the right hemisphere, similar to the declines found in autonomic regulatory sites.

Functional reorganization in neurocognitive networks

HF patients show many cognitive issues, including affective, executive, memory, attention, behavioral, and learning functions [81]. One of the remarkable outcomes that emerged was the appearance of several lateralized abnormal connections anchored at the right caudate and middle frontal gyrus, which presumably contribute to executive deficits in the condition. We speculate that injury in autonomic and respiratory regulatory cerebellar regions may serve decreased functional connections with the right caudate, eventually leading to executive, behavioral, and learning deficits in HF, and reducing the well-known contributions of the basal-ganglia to autonomic regulation [82]. Similarly, damaged sensorimotor regions may also contribute to such functional deficits by abnormally increased (compensatory) interactions with the right middle frontal gyrus.
Other symptoms in HF include an increased incidence of mood disorders [12], which presumably result from regional injury in the prefrontal cortex, para-hippocampal gyrus, cingulate, insula, hippocampus, and cerebellum [15]. In this study, the right amygdala, right hippocampus, and left thalamus (as well as the bilateral insula) in HF showed increased FC with cerebellar sites. These regions reveal exaggerated sympathetic outflow or high metabolic demand, which presumably result from a compensatory mechanism by engaging additional regions with enhanced functional connections. Thus, it may be the case that injury in autonomic and respiratory regulatory cerebellar regions might contribute to increased connections with brain sites serving as high level of mood control in HF. Meanwhile, increased FC between the right hippocampus and vermis III may also contribute to memory loss in HF [15, 83]. The fusiform gyrus is connected with several cerebellar regions, and may affect processing of imaginative fearful objects of anxiety aspects in HF [84].

Deficient processing in attention is common in HF [81], and may be associated with the abnormal network coordination from the posterior parietal cortex (e.g., the posterior cingulate cortex, precuneus, and superior/inferior parietal regions), as observed in our study [85, 86]. Also, the right superior parietal gyrus was observed as a core region, collecting increased connectivity with anterior brain sites within autonomic and respiratory regulatory circuitry. The posterior cingulate cortex and precuneus showed decreased FC with the cerebellum, but showed increased FC with the occipital areas. These findings may suggest mechanisms for the impaired attention and visual processing in HF through abnormal connections with the posterior parietal cortex in the condition [85–87]. Moreover, abnormal FC from the posterior cingulate cortex could contribute to depressive symptoms in the condition [88].

Alterations in topological attributes

Human brain functions are represented by various configurations between local specialization and global integration among brain regional activities [31, 32]. Examining brain network organizational abnormalities can thus provide new insights in exploring disease pathology [89]. Declined regional metabolism within brain tissues and synaptic injury in a disease group may result in disrupted anatomical projections, alter FC, and eventually give rise to an abnormal functional brain network pattern emerging as less effective and reduced regional centrality in core brain areas (with a compensatory increase in other regional central sites), as shown in Alzheimer’s disease [90, 91], Parkinson’s disease [92], and Stroke [93]. Network-level analyses using graph theory in a disease group serve a research framework to explore brain network organization with topological properties [31, 32].

In this study, HF patients showed, across broad regions, predominantly increased topological properties that may result from increased metabolic activity in HF. Increased regional centrality was localized in autonomic and respiratory regions, and bilateral middle temporal pole, inferior occipital gyrus, and right angular gyrus, which may underlie known cognitive issues in the condition. The weighted clustering coefficients (e.g., a measure of regional segregation) and regional efficiency (e.g., an integration measure between two sites in neural information delivery) in HF patients were significantly increased in the precentral, temporal, cerebellar, and right angular regions. Increased regional centrality, segregation, and efficiency of brain networks in HF indicate brain areas unexpectedly engaged by compensatory coordination in the condition, which may represent an exaggerated hub or integrative role for the flow of brain information. Reduced regional centrality in the left para-hippocampal gyrus, bilateral supramarginal gyrus, right thalamus, and vermis VI could contribute to cognitive deficits in HF. Both the para-hippocampal and supramarginal regions are involved in higher-order cognitive/behavioral functions [94], and in integration and interactions involving visual, auditory, and somato-sensory functions.
with adjoining sensory regions [95], respectively. Reduced regional centrality of brain networks in HF shows a diminished hub role for the flow of brain information.

Potential pathological processes

Our findings show that HF brain is not simply affected by localized injury, but also accompanied by abnormal functional network coordination among such damaged areas that serve many of the autonomic, sensorimotor, and cognitive functions deficient in the condition. Several pathological processes may contribute to abnormal functional network properties, including low cardiac output [3] and hypoxia/ischemia processes from sleep disordered breathing issues [96], leading to cerebral perfusion issues. Both processes may result to localized cortical changes, mainly at cortical hub regions. Also, injury to autonomic regions may alter vascular supply to other cortical sites that may induce secondary damage to other brain areas across the brain, and eventually may result in abnormal functional brain network in the condition.

Limitations

Several limitations of this study should be acknowledged. We evaluated individual brain networks by splitting the whole-brain into 116 regions, as a widely used parcellation scheme in brain network studies. Further studies are required to compare the current findings using different parcellation schemes, since their uses could exhibit different graph-theoretical results, based on variable regions of interest [97–100]. Also, all subjects were instructed not to focus on any specific thoughts during scanning, we could not ensure about this issue, and could be considered as potential limitation. However, heart rate was carefully monitored in all subjects during the resting-state functional MRI, and none of subjects included here showed significant heart rate fluctuation, indicating that subjects followed our instruction for not focusing on specific thoughts during the resting-state functional MRI.

Conclusions

Heart failure patients show resting-state spontaneous brain dysfunction between multiple sites, and autonomic, cognitive, and affective deficits may stem from the altered FC and brain network organization. The altered FC in HF is largely lateralized to the right hemisphere, which may result from previously-identified lateralized tissue changes in the condition. These increased and decreased FC deficits may contribute to higher morbidity and mortality in the condition. The adverse clinical outcomes likely result from the prominent structural changes in both axons and nuclear structures reported earlier in HF; protecting neural tissue may improve functional network integrity, and thus, reduce morbidity and mortality and increase quality of life in the condition.

Supporting Information

S1 Fig. Correlation of BMI, LVEF, PSQI, ESS, BAI, or BDI-II with FC. Weak relationship trend between each variables and functional connections. Blue and red color represents negative and positive relationships, respectively. Other figure conventions are same as in Figs 2 and 3.

(DOCX)
Acknowledgments

We thank Mrs. Rebecca K. Harper and Mrs. Karen Harada for assistance with data collection. This research was supported by National Institutes of Health R01 NR-013625 and R01 NR-014669.

Author Contributions

Conceived and designed the experiments: RK MW BP. Performed the experiments: RK MW BP JP BR. Analyzed the data: BP. Contributed reagents/materials/analysis tools: BP RK. Wrote the paper: BP, RK, RH, GF, BR.

References

1. Almeida OP, Flicker L. The mind of a failing heart: a systematic review of the association between congestive heart failure and cognitive functioning. Intern Med J. 2001; 31: 290–295. PMID: 11512600
2. Jiang W, Kuchibhatla M, Clary GL, Cuffe MS, Christopher EJ, Alexander JD, et al. Relationship between depressive symptoms and long-term mortality in patients with heart failure. Am Heart J. 2007; 154: 102–108. PMID: 17584561
3. Woo MA, Macey PM, Keens PT, Kumar R, Fonarow GC, Hamilton MA, et al. Functional abnormalities in brain areas that mediate autonomic nervous system control in advanced heart failure. J Card Fail. 2005; 11: 437–446. PMID: 16105635
4. Woo MA, Macey PM, Keens PT, Kumar R, Fonarow GC, Hamilton MA, et al. Aberrant central nervous system responses to the Valsalva maneuver in heart failure. Congest Heart Fail. 2007; 13: 29–35. PMID: 17272960
5. Mann D. Pathophysiology of heart failure. In: Libby P B R, Mann DL, Zipes DP, editor. Braunwald’s heart disease: a textbook of cardiology. Burlington, MA: Saunders Elsevier; 2008. p. 541–560.
6. Redeker NS, Muench U, Zucker MJ, Walsleben J, Gilbert M, Freudenberger R, et al. Sleep disordered breathing, daytime symptoms, and functional performance in stable heart failure. Sleep. 2010; 33: 551–560. PMID: 20394325
7. Woo MA, Fonarow GC. Sleep-disordered Breathing in Heart Failure. Curr Treat Options Cardiovasc Med. 2003; 5: 459–467. PMID: 14575623
8. Petrucci RJ, Truesdell KC, Carter A, Goldstein NE, Russell MM, Dikkes D, et al. Cognitive dysfunction in advanced heart failure and prospective cardiac assist device patients. Ann Thorac Surg. 2006; 81: 1738–1744. PMID: 16631665
9. Pressler SJ, Kim J, Riley P, Ronis DL, Gradus-Pizio I. Memory dysfunction, psychomotor slowing, and decreased executive function predict mortality in patients with heart failure and low ejection fraction. J Card Fail. 2010; 16: 750–760. doi:10.1016/j.cardfail.2010.04.007 PMID: 20797599
10. Riegel B, Bennett JA, Davis A, Carlson B, Montague J, Robin H, et al. Cognitive impairment in heart failure: issues of measurement and etiology. Am J Crit Care. 2002; 11: 529–528. PMID: 12425402
11. Trojano L, Antonelli Incalzi R, Acanfora D, Picone C, Meccoci P, Rengo F, et al. Cognitive impairment: a key feature of congestive heart failure in the elderly. J Neurol. 2003; 250: 1456–1463. PMID: 14673579
12. Rumsfeld JS, Havranek E, Masoudi FA, Peterson ED, Jones P, Tooley JF, et al. Depressive symptoms are the strongest predictors of short-term declines in health status in patients with heart failure. J Am Coll Cardiol. 2003; 42: 1811–1817. PMID: 14642693
13. Kumar R, Woo MA, Macey PM, Fonarow GC, Hamilton MA, Harper RM. Brain axonal and myelin evaluation in heart failure. J Neurol Sci. 2011; 307: 106–113. doi:10.1016/j.jns.2011.04.028 PMID: 21612797
14. Woo MA, Palomares JA, Macey PM, Fonarow GC, Harper RM, Kumar R. Global and regional brain mean diffusivity changes in patients with heart failure. J Neurosci Res. 2015; 93: 678–685. doi: 10.1002/jnr.23525 PMID: 25502071
15. Woo MA, Kumar R, Macey PM, Fonarow GC, Harper RM. Brain injury in autonomic, emotional, and cognitive regulatory areas in patients with heart failure. J Card Fail. 2009; 15: 214–223. doi: 10.1016/j.cardfail.2008.10.020 PMID: 19327823
16. Woo MA, Macey PM, Fonarow GC, Hamilton MA, Harper RM. Regional brain gray matter loss in heart failure. J Appl Physiol (1985). 2003; 95: 677–684.
17. Ogren JA, Macey PM, Kumar R, Fonarow GC, Hamilton MA, Harper RM, et al. Impaired cerebellar and limbic responses to the valsala maneuver in heart failure. Cerebellum. 2012; 11: 931–938. doi: 10.1007/s12311-012-0361-y PMID: 22370874

18. Friston KJ. Functional and effective connectivity in neuroimaging: a synthesis. Hum Brain Mapp. 1994; 2: 56–78.

19. Cordes D, Haughton VM, Arfanakis K, Wendt GJ, Turski PA, Moritz CH, et al. Mapping functionally related regions of brain with functional connectivity MR imaging. AJNR Am J Neuroradiol. 2000; 21: 1636–1644. PMID: 11039342

20. Lowe MJ, Mock BJ, Sorenson JA. Functional connectivity in single and multislice echoplanar imaging using resting-state fluctuations. Neuroimage. 1998; 7: 119–132. PMID: 9558644

21. Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn Reson Med. 1995; 34: 537–541. PMID: 8524021

22. Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci. 2007; 8: 700–711. PMID: 17704812

23. De Luca M, Beckmann CF, De Stefano N, Matthews SM. fMRI resting state networks define distinct modes of long-distance interactions in the human brain. Neuroimage. 2006; 29: 1359–1367. PMID: 16260155

24. Damoiseaux JS, Rombouts SA, Barkhof F, Scheltens P, Stam CJ, Rombouts SA, et al. Consistent resting-state networks across healthy subjects. Proc Natl Acad Sci U S A. 2006; 2006: 103: 13848–13853. PMID: 17543634

25. Beckmann CF, Smith SM. Tensorial extensions of independent component analysis for multisubject FMRI analysis. Neuroimage. 2005; 25: 294–311. PMID: 15734364

26. Fox MD, Greicius M. Clinical applications of resting state functional connectivity. Front Syst Neurosci. 2010; 4: 19. doi: 10.3389/Insys.2010.00019 PMID: 20592951

27. Sadaghiani S, Kleinschmidt A. Functional interactions between intrinsic brain activity and behavior. Neuroimage. 2013; 80: 379–386. doi: 10.1016/j.neuroimage.2013.04.100 PMID: 23639291

28. Laird AR, Eickhoff SB, Rottschey C, Bzdok D, Ray KL, Fox PT. Networks of task co-activations. Neuroimage. 2006; 2006: 30: 505–514. doi: 10.1016/j.neuroimage.2005.07.037 PMID: 16260155

29. Smith SM, Fox PT, Miller KL, Glahn DC, Fox PM, Mackay CE, et al. Correspondence of the brain’s functional architecture during activation and rest. Proc Natl Acad Sci U S A. 2009; 106: 13040–13045. doi: 10.1073/pnas.0905267106 PMID: 19620724

30. Inman CS, James GA, Hamann S, Rajendra JK, Pagnoni G, Butler AJ. Altered resting-state effective connectivity of fronto-parietal motor control systems on the primary motor network following stroke. Neuroimage. 2012; 2012: 59: 227–237. doi: 10.1016/j.neuroimage.2011.07.083 PMID: 21839174

31. Bullmore E, Sporns O. Complex brain networks: graph theoretical analysis of structural and functional systems. Nat Rev Neurosci. 2009; 2009: 10: 186–198. doi: 10.1038/nrn2575 PMID: 19190637

32. Bullmore E, Sporns O. The economy of brain network organization. Nat Rev Neurosci. 2012; 13: 336–349. doi: 10.1038/nrn3214 PMID: 22498897

33. Sporns O, Tononi G, Edelman GM. Theoretical neuroanatomy: relating anatomical and functional connectivity in graphs and cortical connection matrices. Cereb Cortex. 2000; 2000: 10: 127–141. PMID: 10667981

34. Watts DJ, Strogatz SH. Collective dynamics of ‘small-world’ networks. Nature. 1998; 393: 440–442. PMID: 9623998

35. Bassett DS, Bullmore E, Verchinski BA, Mattay VS, Weinberger DR, Meyer-Lindenberg A. Hierarchical organization of human cortical networks in health and schizophrenia. J Neurosci. 2008; 28: 9239–9248. doi: 10.1523/JNEUROSCI.1929-08.2008 PMID: 18784304

36. Gong G, Rosa-Neto P, Carbonell F, Chen ZJ, He Y, Evans AC. Age- and gender-related differences in the cortical anatomical network. J Neurosci. 2009; 29: 15684–15693. doi: 10.1523/JNEUROSCI.2308-09.2009 PMID: 20016083

37. Hagmann P, Kurant M, Gigandet X, Thiran P, Wedeen VJ, Meuli R, et al. Mapping human whole-brain structural networks with diffusion MRI. PLOS One. 2007; 2: e597. PMID: 17611629

38. He Y, Chen ZJ, Evans AC. Small-world anatomical networks in the human brain revealed by cortical thickness from MRI. Cereb Cortex. 2007; 17: 2407–2419. PMID: 17204824

39. Iturria-Medina Y, Sotero RC, Canales-Rodríguez EJ, Aleman-Gomez Y, Melie-Garcia L. Studying the human brain anatomical network via diffusion-weighted MRI and Graph Theory. Neuroimage. 2008; 40: 1064–1076. doi: 10.1016/j.neuroimage.2007.10.060 PMID: 18272400
41. Achard S, Salvador R, Whitzer B, Suckling J, Bullmore E. A resilient, low-frequency, small-world human brain functional network with highly connected association cortical hubs. J Neurosci. 2006; 26: 63–72. PMID:16399673
42. Eguiluz VM, Chialvo DR, Cecchi GA, Baliki M, Apkarian AV. Scale-free brain functional networks. Phys Rev Lett. 2005; 94: 018102. PMID:15698136
43. Salvador R, Suckling J, Coleman MR, Pickard JD, Menon D, Bullmore E. Neurophysiological architecture of functional magnetic resonance images of human brain. Cereb Cortex. 2005; 15: 1332–1342. PMID:15635061
44. Stam CJ. Functional connectivity patterns of human magnetoencephalographic recordings: a ‘small-world’ network? Neurosci Lett. 2004; 355: 25–28. PMID:14729226
45. Stam CJ, Reijneveld JC. Graph theoretical analysis of complex networks in the brain. Nonlinear Biomed Phys. 2007; 1: 3. PMID:17908336
46. Crossley NA, Mechelli A, Scott J, Carletti F, Fox PT, McGuire P, et al. The hubs of the human connectome are generally implicated in the anatomy of brain disorders. Brain. 2014; 137: 2382–2395. doi:10.1093/brain/awu132 PMID: 25057133
47. Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, et al. 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation. 2009; 119: 1977–2016. doi:10.1161/CIRCULATIONAHA.109.192064 PMID: 19324967
48. Radford MJ, Arnold JM, Bennett SJ, Cinquegrani MP, Cleland JG, Havranek EP, et al. ACC/AHA key data elements and definitions for measuring the clinical management and outcomes of patients with chronic heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Heart Failure Clinical Data Standards): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Failure Society of America. Circulation. 2005; 112: 1888–1916. PMID:16162914
49. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol. 1988; 56: 893–897. PMID:3204199
50. Beck AT, Steer RA, Ball R, Ranieri W. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. J Pers Assess. 1996; 67: 588–597. PMID:8991972
51. Carpenter JS, Andrykowski MA. Psychometric evaluation of the Pittsburgh Sleep Quality Index. J Psychosom Res. 1998; 45: 5–13. PMID:9720850
52. Johns MW. Reliability and factor analysis of the Epworth Sleepiness Scale. Sleep. 1992; 15: 376–381. PMID:1519015
53. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005; 53: 695–699. PMID:15817019
54. Friston KJ, Holmes AP, Worsley KJ, Poline JP, Frith CD, Frackowiak RS. Statistical parametric maps in functional imaging: a general linear approach. Hum Brain Mapp. 1994; 2: 189–210.
55. Rorden C, Karnath HO, Bonilha L. Improving lesion-symptom mapping. J Cogn Neurosci. 2007; 19: 1081–1088. PMID:17583985
56. van den Heuvel MP, Stam CJ, Boersma M, Hulshoff Pol HE. Small-world and scale-free organization of voxel-based resting-state functional connectivity in the human brain. Neuroimage. 2008; 43: 528–539. doi:10.1016/j.neuroimage.2008.08.010 PMID: 18786642
57. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage. 2002; 15: 273–289. PMID: 11771995
58. Weissenbacher A, Kasess C, Gerstl F, Lanzenberger R, Moser E, Windischberger C. Correlations and anticorrelations in resting-state functional connectivity MRI: a quantitative comparison of preprocessing strategies. Neuroimage. 2009; 47: 1408–1416. doi: 10.1016/j.neuroimage.2009.05.005 PMID: 19442749
59. Power JD, Mitra A, Laumann TO, Snyder AZ, Schlaggar BL, Petersen SE. Methods to detect, characterize, and remove motion artifact in resting state fMRI. Neuroimage. 2014; 84: 320–341. doi: 10. 1016/j.neuroimage.2013.08.048 PMID: 23994314
60. Yan CG, Cheung B, Kelly C, Colcombe S, Craddock RC, Di Martino A, et al. A comprehensive assessment of regional variation in the impact of head micromovements on functional connectomics. Neuroimage. 2013; 76: 183–201. doi:10.1016/j.neuroimage.2013.03.004 PMID: 23499792
61. Van Dijk KR, Sabuncu MR, Buckner RL. The influence of head motion on intrinsic functional connectivity MRI. Neuroimage. 2012; 59: 431–438. doi: 10.1016/j.neuroimage.2011.07.044 PMID: 21810475

62. Rubinov M, Sporns O. Complex network measures of brain connectivity: uses and interpretations. Neuroimage. 2010; 52: 1059–1069. doi: 10.1016/j.neuroimage.2009.10.003 PMID: 19819337

63. Genovese CR, Lazar NA, Nichols T. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. Neuroimage. 2002; 15: 870–878. PMID: 11906227

64. Latora V, Marchiori M. Efficient behavior of small-world networks. Phys Rev Lett. 2001; 87: 198701. PMID: 11690461

65. Achard S, Bullmore E. Efficiency and cost of economical brain functional networks. PLOS Comput Biol. 2007; 3: e17. PMID: 17274684

66. Nichols TE, Holmes AP. Nonparametric permutation tests for functional neuroimaging: a primer with examples. Hum Brain Mapp. 2002; 15: 1–25. PMID: 11747097

67. Genovese CR, Lazar NA, Nichols T. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. Neuroimage. 2002; 15: 870–878. PMID: 11906227

68. Notarius CF, Spaak J, Morris BL, Floras JS. Comparison of muscle sympathetic activity in ischemic and nonischemic heart failure. J Card Fail. 2007; 13: 470–475. PMID: 17675061

69. Cechetto DF, Chen SJ. Subcortical sites mediating sympathetic responses from insular cortex in rats. Am J Physiol. 1990; 258: R245–255. PMID: 2301638

70. Oppenheimer SM, Gelb A, Girvin JP, Hachinski VC. Cardiovascular effects of human insular cortex stimulation. Neurology. 1992; 42: 1727–1732. PMID: 1513461

71. Oppenheimer SM, Kedem G, Martin WM. Left-insular cortex lesions perturb cardiac autonomic tone in humans. Clin Auton Res. 1996; 6: 131–140. PMID: 8832121

72. Henderson LA, Richard CA, Macey PM, Runquist ML, Yu PL, Galons JP, et al. Functional magnetic resonance signal changes in neural structures to baroreceptor reflex activation. J Appl Physiol (1985). 2004; 96: 693–703.

73. Banzett RB, Mulnier HE, Murphy K, Rosen SD, Wise RJ, Adams L. Breathlessness in humans activates insular cortex. Neuroreport. 2000; 11: 2117–2120. PMID: 10923655

74. Critchley HD. Neural mechanisms of autonomic, affective, and cognitive integration. J Comp Neurol. 2005; 493: 154–166. PMID: 16254997

75. Critchley HD, Mathias CJ, Josephs O, O’Doherty J, Zanini S, Dewar BK, et al. Human cingulate cortex and autonomic control: converging neuroimaging and clinical evidence. Brain. 2003; 126: 2139–2152. PMID: 12821513

76. Reekie YL, Braesicke K, Man MS, Roberts AC. Uncoupling of behavioral and autonomic responses after lesions of the primate orbitofrontal cortex. Proc Natl Acad Sci U S A. 2008; 105: 9787–9792. doi: 10.1073/pnas.0800417105 PMID: 18621690

77. Wong SW, Masse N, Kimmerly DS, Menon RS, Shoemaker JK. Ventral medial prefrontal cortex and cardiovascular control in conscious humans. Neuroimage. 2007; 35: 698–708. PMID: 17291781

78. Holmes MJ, Cotter LA, Arendt HE, Cass SP, Yates BJ. Effects of lesions of the caudal cerebellar vermis on cardiovascular regulation in awake cats. Brain Res. 2002; 938: 62–72. PMID: 12031536

79. Lutherer LO, Williams JL. Stimulating fastigial nucleus pressor region elicits patterned respiratory responses. Am J Physiol. 1986; 250: R418–426. PMID: 2869699

80. Woo MA, Yadav SK, Macey PM, Fonarow GC, Harper RM, Kumar R. Brain metabolites in autonomic regulatory insular sites in heart failure. J Neurol Sci. 2014; 346: 271–275. doi: 10.1016/j.jns.2014.09.006 PMID: 25248953

81. Ogren JA, Fonarow GC, Woo MA. Cerebral impairment in heart failure. Curr Heart Fail Rep. 2014; 11: 321–329. doi: 10.1007/s11897-014-0211-y PMID: 25001614

82. Pazoo JH, Belforte JE. Basal ganglia and functions of the autonomic nervous system. Cell Mol Neurobiol. 2002; 22: 645–654. PMID: 12585684

83. Woo MA, Ogren JA, Abuzeid CM, Macey PM, Sairafian KG, Saharan PS, et al. Regional hippocampal damage in heart failure. Eur J Heart Fail. 2015; 17: 494–500. doi: 10.1002/ejhf.241 PMID: 25704495

84. Frick A, Howner K, Fischer H, Kristiansson M, Furmark T. Altered fusiform connectivity during processing of fearful faces in social anxiety disorder. Transl Psychiatry. 2013; 3: e312. doi: 10.1038/tj.2013.85 PMID: 24105443

85. Chan RC, Shum D, Toulopoulou T, Chen EY. Assessment of executive functions: review of instruments and identification of critical issues. Arch Clin Neuropsychol. 2008; 23: 201–216. PMID: 18096360
86. Cohen R, Salloway S, Sweet L. Neuropsychiatric aspects of disorders of attention. In: Yudofsky SC, Hales RE, eds Textbook of Neuropsychiatry Washington, DC: American Psychiatric Press. 2008: 405–444.

87. Utevsky AV, Smith DV, Huettel SA. Precuneus is a functional core of the default-mode network. J Neurosci. 2014; 34: 932–940. doi: 10.1523/JNEUROSCI.4227-13.2014 PMID: 24431451

88. Monti RP, Hellyer P, Sharp D, Leech R, Anagnostopoulos C, Montana G. Estimating time-varying brain connectivity networks from functional MRI time series. Neuroimage. 2014; 103: 427–443. doi: 10.1016/j.neuroimage.2014.07.033 PMID: 25107854

89. Bassett DS, Bullmore ET. Human brain networks in health and disease. Curr Opin Neurol. 2009; 22: 340–347. doi: 10.1097/WCO.0b013e32832d93dd PMID: 19494774

90. Wang J, Wang X, He Y, Yu X, Wang H, He Y. Apolipoprotein E epsilon4 modulates functional brain connectome in Alzheimer's disease. Hum Brain Mapp. 2015; 36: 1828–1846. doi: 10.1002/hbm.22740 PMID: 25619771

91. Liu Y, Yu C, Zhang X, Liu J, Duan Y, Alexander-Bloch AF, et al. Impaired long distance functional connectivity and weighted network architecture in Alzheimer's disease. Cereb Cortex. 2014; 24: 1422–1435. doi: 10.1093/cercor/bhs410 PMID: 23314940

92. Olde Dubbelink KT, Hillebrand A, Stoffers D, Deijen JB, Twisk JW, Stam CJ, et al. Disrupted brain network topology in Parkinson's disease: a longitudinal magnetoencephalography study. Brain. 2014; 137: 197–207. doi: 10.1093/brain/awt316 PMID: 24271324

93. Yin D, Song F, Xu D, Sun L, Men W, Zang L, et al. Altered topological properties of the cortical motor-related network in patients with subcortical stroke revealed by graph theoretical analysis. Hum Brain Mapp. 2014; 35: 3343–3359. doi: 10.1002/hbm.22406 PMID: 24223371

94. Aggleton JP, Vann SD, Saunders RC. Projections from the hippocampal region to the mammillary bodies in macaque monkeys. Eur J Neurosci. 2005; 22: 2516–2530. PMID: 16307594

95. Stoeckel C, Gough PM, Watkins KE, Devlin JT. Supramarginal gyrus involvement in visual word recognition. Cortex. 2009; 45: 1091–1096. doi: 10.1016/j.cortex.2008.12.004 PMID: 19232536

96. Ferrier K, Campbell A, Yee B, Richards M, O'Meeghan T, Weatherall M, et al. Sleep-disordered breathing occurs frequently in stable outpatients with congestive heart failure. Chest. 2005; 128: 2116–2122. PMID: 16236863

97. Fornito A, Zalesky A, Bullmore ET. Network scaling effects in graph analytic studies of human resting-state fMRI data. Front Syst Neurosci. 2010; 4: 22. doi: 10.3389/fnsys.2010.00022 PMID: 20592949

98. Telesford QK, Morgan AR, Hayasaka S, Simpson SL, Barret W, Kraft RA, et al. Reproducibility of graph metrics in fMRI networks. Front Neuroinform. 2010; 4: 117. doi: 10.3389/fninf.2010.00117 PMID: 21165174

99. Wang J, Wang L, Zang Y, Yang H, Tang H, Gong Q, et al. Parcellation-dependent small-world brain functional networks: a resting-state fMRI study. Hum Brain Mapp. 2009; 30: 1511–1523. doi: 10.1002/hbm.20623 PMID: 18649353

100. Zalesky A, Fornito A, Harding IH, Cocchi L, Yucel M, Pantelis C, et al. Whole-brain anatomical networks: does the choice of nodes matter? Neuroimage. 2010; 50: 970–983. doi: 10.1016/j.neuroimage.2009.12.027 PMID: 20035887