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A systematic review on the quantitative relationship between structural and functional network connectivity strength in mammalian brains

Milou Straathof[1], Michel RT Sinke[1], Rick M Dijkhuizen[1] and Willem M Otte[1,2]; on behalf of the TACTICS consortium*

Abstract

The mammalian brain is composed of densely connected and interacting regions, which form structural and functional networks. An improved understanding of the structure–function relation is crucial to understand the structural underpinnings of brain function and brain plasticity after injury. It is currently unclear how functional connectivity strength relates to structural connectivity strength. We obtained an overview of recent papers that report on correspondences between quantitative functional and structural connectivity measures in the mammalian brain. We included network studies in which functional connectivity was measured with resting-state fMRI, and structural connectivity with either diffusion-weighted MRI or neuronal tract tracers. Twenty-seven of the 28 included studies showed a positive structure–function relationship. Large inter-study variations were found comparing functional connectivity strength with either quantitative diffusion-based (correlation coefficient (r) ranges: 0.18–0.82) or neuronal tracer-based structural connectivity measures ($r = 0.24$–0.74). Two functional datasets demonstrated lower structure–function correlations with neuronal tracer-based ($r = 0.22$ and $r = 0.30$) than with diffusion-based measures ($r = 0.49$ and $r = 0.65$). The robust positive quantitative structure–function relationship supports the hypothesis that structural connectivity provides the hardware from which functional connectivity emerges. However, methodological differences between the included studies complicate the comparison across studies, which emphasize the need for validation and standardization in brain structure–function studies.

Keywords

Brain, diffusion magnetic resonance imaging, functional magnetic resonance imaging, network connectivity, neuronal tract-tracers

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Introduction

The brain is a complex system composed of connected and interacting regions at the micro-, meso- and macro-level. Network science offers unique opportunities to assess the healthy and diseased brain while taking this complexity into account. In this field, the brain is regarded as a structural and functional network in which single voxels, or multiple voxels combined into regions, serve as the network nodes, and structural and functional connectivity represent the edges.[1] These edges might be either binary (i.e. present or absent) or weighted (i.e. indication of connectivity strength). The structural and functional organization

[1]Biomedical MR Imaging and Spectroscopy Group, Center for Image Sciences, University Medical Center Utrecht and Utrecht University, Utrecht, the Netherlands
[2]Department of Pediatric Neurology, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, the Netherlands
*Members of the TACTICS consortium are listed in the Acknowledgments section.

Corresponding author:
Milou Straathof, Biomedical MR Imaging and Spectroscopy Group, Center for Image Sciences, University Medical Center Utrecht and Utrecht University, Yalelaan 2, Utrecht 3584 CM, the Netherlands.
Email: M.Straathof-2@umcutrecht.nl

of brain networks can be studied in a unique translational way in animals and humans using non-invasive magnetic resonance imaging (MRI) techniques.[2] Today, the standard non-invasive neuroimaging techniques to characterize whole-brain functional and structural networks in vivo are resting-state functional MRI (rs-fMRI) and diffusion-weighted MRI (DW-MRI)-based tractography, respectively. Although many studies have characterized features of functional and structural networks in isolation, there is limited knowledge on their mutual relationship.

Over the years, rs-fMRI has been increasingly used to assess functional connectivity of the brain. Spontaneous low-frequency fluctuations in the blood oxygenation level-dependent (BOLD) signal, reflective of neuronal signaling, have been measured in humans and animals.[3] Brain regions with patterns of correlated fluctuations in the time-domain are considered functionally connected.[4] The correlation coefficient between BOLD signal fluctuations in different brain regions over time offers a quantitative measure of the strength of a functional connection. Positive correlation coefficients reflect synchronization of the underlying neuronal signals. Based on clusters of functionally connected network regions, consistent resting-state networks have been identified,[5,6] such as the default mode network.[7] The default mode network is a well-characterized and frequently investigated resting-state network in humans, consisting of regions in the parietal and prefrontal cortex,[8] of which an equivalent network has been demonstrated in non-human primates[9] and rodents.[10,11] Disturbances in this network are linked to multiple brain disorders, including Alzheimer's disease, autism, schizophrenia, depression, chronic pain and others.[12] Interestingly, regions within the default mode network which are functionally firmly connected, do not always have strong direct structural connections.[13,14]

Functional connectivity reflects neuronal synchronization between brain regions, which presumably requires some form of structural connectivity. Structural connectivity can be measured non-invasively with tractography from post-processing of DW-MRI data. DW-MRI is sensitized to the random diffusion of water molecules in tissue.[15] Tractography reconstructs the white matter fiber geometry across the brain by propagating streamlines based on the water diffusion preference.[16] The generated streamlines between two areas of interest can be considered as diffusion-based structural connectivity. Tractography-based (e.g. number of connecting streamlines) or integrity-related (e.g. fractional anisotropy (FA) across connecting streamlines) measures can provide quantitative information on diffusion-based structural connectivity strength. The main assumption of DW-MRI and subsequent tractography is that the directionality of water diffusion reflects the underlying organization of white matter tracts.[17] Hence, DW-MRI is an indirect method to infer white matter tracts of the brain from tissue water diffusion, often with suboptimal anatomical accuracy.[18,19] In animals, structural connectivity can also be measured invasively with the use of neuronal tracers.[20] Several anterograde and retrograde tracers are available, which are taken up by neurons and axonally transported, allowing assessment of the location, directionality and targets of neuronal projections.[21,22] Structural connections measured with neuronal tracers reflect axonal projections between the injection area and the connected regions. The amount of tracer detected in the connected regions provides a quantitative measure of neuronal tracer-based structural connectivity strength.

Recently, rs-fMRI and DW-MRI have been combined to investigate the relationship between functional and structural connectivity, to determine if and how the structural network constrains, maintains and regulates the functional network.[23] It remains unclear how a relatively stable structural network supports fast dynamic functional connectivity, and how functional plasticity influences the structural network on a slower time-scale. An improved understanding of this structure–function relationship in the healthy brain is crucial to understand the structural underpinnings of abnormal functional connectivity. Abnormal functional connectivity is manifested in many neurological and psychiatric disorders and also plays a critical role in the brain's capacity to recover from injury. Abnormal neuronal functioning may be the result of damage to specific functional areas, or damage to the structural connections between functional areas. Combined assessment of structural and functional connectivity measures and the structure–function correlation may thus provide unique insights into the complex neurobiology of brain disorders. Indeed, measurement of the structure–function relationship has already shown added value, compared to measurement of only structural or functional connectivity, in relating MRI findings to disease outcome in idiopathic generalized epilepsy patients.[24] In addition, structure–function coupling may be a potential novel biomarker in cerebrovascular disorders, since the structure–function coupling has been shown to relate to functional motor outcome in stroke patients.[25] Structural connectivity shapes functional connectivity if the functional data are characterized within long periods of relative rest (order of minutes) without a specific activating task or stimulation.[26] The structure–function relationship in brain networks has mostly been investigated qualitatively, e.g. structural connection presence or absence in comparison to functional connection presence or

absence.[23] These studies have shown that functionally connected network regions are essentially shaped by underlying structural connectivity, although functional connections were also found to be present between regions without direct structural connections.[13,27,28] In addition, removing the corpus callosum in monkeys reduced interhemispheric functional connectivity, but not when other smaller interhemispheric structural connections were still intact.[29] This indicates the importance of indirect structural connections (e.g. via subcortical structures) for interhemispheric functional connectivity. Although the presence of a functional connection may depend on the presence of a direct or indirect structural connection, the strength of a functional connection does not need to be directly related to the strength of those structural connections, but may also depend on mental brain state.[30,31] However, quantitative structure–function analyses that incorporate connectivity strengths have received much less attention, possibly because inferring structural connectivity strength from diffusion-based tracts is not as straightforward as calculating functional connectivity strength. Nevertheless, these quantitative structure–function analyses in whole-brain networks enable direct comparison between the strength of functional and structural connections and may provide additional information about the structure–function relationship, which is the focus of the current review.

A few studies that applied abovementioned quantitative approach, have demonstrated partial positive correspondence between functional connectivity and diffusion-based structural measures.[28,32] A positive structure–function relation in such a quantitative approach means that stronger structural connections coincide with stronger functional connections. So there is a high topological correspondence between the structural and functional network. In comparison, a negative structure–function relation would indicate strong structural but weak functional connectivity or the opposite (i.e. low topological correspondence). Although strong anatomical and weak functional connectivity between regions almost never co-exist, weak anatomical combined with strong functional connectivity is present in the brain.[33] Similar positive correspondences have been reported in the comparison of functional networks with neuronal tracer networks.[11,34] However, the described correlation between functional and structural connectivity strength varies substantially over studies. Whether this is due to differences in methodology or differences in emphasis on distinct levels of brain organization (across species), is unknown. Whereas DW-MRI measures structural connections at the macroscopic level of larger white matter bundles, neuronal tracers characterize structural connectivity at the mesoscopic level.[18,35] Therefore, to clarify the variation in structure–function relationships, it is important to also understand the correlation between diffusion-based and neuronal tracer-based structural connectivity strength.

In this paper, we systematically reviewed the literature to obtain an overview of publications that report on quantitative correlations between functional and structural network connectivity strength in the mammalian brain. We included network studies in which functional connectivity strength was measured with rs-fMRI, and structural connectivity strength was measured with either DW-MRI or with neuronal tract tracers. In this systematic review, we addressed the following questions at the network level: (I) To what extent is functional connectivity strength correlated to diffusion-based structural connectivity strength? (II) To what extent is functional connectivity strength correlated to neuronal tracer-based structural connectivity strength? And (III) to what extent is diffusion-based connectivity strength correlated with neuronal tracer-based connectivity strength?

Materials and methods

Information source and searches

We performed our literature search in the database PubMed (NCBI), using three separate queries for the three comparisons of interest. First, we searched for publications on the quantitative relationship between functional connectivity strength and DW-MRI-based structural connectivity measures. Second, we identified all publications on the quantitative relationship between functional connectivity strength and neuronal tracer-based structural measures. Third, we mapped publications on the quantitative relationship between DW-MRI-based and neuronal tracer-based structural measures. Our PubMed search queries were as follows:

Search 1: (connectome[tiab] OR (''structural connectivity''[tiab] OR ''anatomical connectivity''[tiab] AND ''functional connectivity''[tiab])) AND (''Diffusion Magnetic Resonance Imaging''[Mesh] OR DTI[tiab] OR ''Diffusion tensor imaging''[tiab] OR tractography[tiab] OR streamlines[tiab]) AND (''resting-state''[tiab] OR fMRI[tiab] OR ''functional MRI''[tiab]).

Search 2: (connectome[tiab] OR (''structural connectivity''[tiab] OR ''anatomical connectivity''[tiab] AND ''functional connectivity''[tiab])) AND (histology[tiab] OR tracer[tiab] OR ''axonal tract tracing''[tiab] OR ''anatomical projections''[tiab] OR ''anatomical connections''[tiab] OR tracing[tiab] OR ''neuronal tracer''[tiab]) AND (''resting-state''[tiab] OR fMRI[tiab] OR ''functional MRI''[tiab]).

Search 3: (connectome[tiab] OR "brain network"[tiab] OR "whole brain"[tiab] OR "anatomical connections"[tiab]) AND ("Diffusion Magnetic Resonance Imaging"[Mesh] OR DTI[tiab] OR "Diffusion tensor imaging"[tiab] OR tractography[tiab] OR streamlines[tiab]) AND (histology[tiab] OR tracer[tiab] OR "axonal tract tracing"[tiab] OR "anatomical projections"[tiab] OR tracing[tiab] OR "neuronal tracer"[tiab]).

The search date was July 24, 2018. Additional studies that could be included were identified in reference lists of the included full-text articles found in the initial search.

Inclusion criteria

We only included studies that measured a quantitative relationship between functional and structural connectivity in brain networks, i.e. correlating the strength of a functional connection to a quantitative structural connectivity measure, and did not include studies in which this relationship was measured qualitatively. In addition, we included studies correlating diffusion-based and neuronal tracer-based structural connectivity strengths.

Studies describing connectivity between single brain region pairs were not included in this systematic review. We also did not include studies that characterized functional networks with electroencephalography or magneto encephalography. These acquisitions have high temporal resolution but lack sufficient spatial resolution to accurately compare functional connectivity strengths with structural connectivity strengths.

Studies meeting the following criteria were included:

- *Study population*: Mammals, healthy human subjects or animals, of any age.
- *Study design*: Functional connectivity measured with rs-fMRI, and structural connectivity measured with DW-MRI and/or neuronal tract tracing.
- *Brain network resolution*: The structure–function relationship assessed at a regional or voxel level in the whole brain or in the default mode network specifically.
- *Outcome*: Correlations between quantitative functional structural connectivity measures.

Results and discussion

Study selection

The flow diagrams for the study selection for the three different comparisons are shown in Figure 1. In total, 29 studies met our inclusion criteria. First, for the relationship between resting-state functional connectivity and diffusion-based structural connectivity, we subdivided the articles mapping whole-brain networks ($n = 16$)[8,28,32,36–48,] and the articles mapping the default mode network ($n = 4$).[49–52] Second, the relationship between resting-state functional connectivity and neuronal tracer-based structural connectivity was investigated in seven studies.[11,34,46,53–56] We excluded one study[54] because the same dataset was used in another included study,[34] resulting in six included studies. Third, the relationship between diffusion-based and neuronal tracer-based structural connectivity strength was described in four studies.[46,57–59] One of the included studies investigated all three comparisons.[46] Therefore, the total amount of papers included in this review is 28.

Because of the relative large heterogeneity between study methodology and outcomes, no meta-analyses were performed, because aggregated summary results would consequently be biased due to this heterogeneity.

To what extent is functional connectivity strength correlated to diffusion-based structural connectivity strength?

An overview of the extracted data used for the comparison between resting-state functional connectivity and diffusion-based structural connectivity is shown for the whole brain (Table 1). The data for the default mode network are separately shown in Table 2. At the whole-brain level (Figure 2), all studies reported a positive correlation between functional connectivity strength and diffusion-based structural connectivity strength. This supports the hypothesis that structural network connectivity, at least partially, shapes functional network connectivity.[23,60] We found a similar positive structure–function relationship in the default mode network (Figure 3). Changes in the structure–function relationship in the default mode network have been associated with Alzheimer's disease[42] and schizophrenia,[49] stressing the importance of assessing this relationship at different levels in the brain to improve our understanding of the pathogenesis of brain disorders.

However, as seen in Figures 2 and 3, the reported correlation coefficient varies substantially between studies. This large variation may be explained by several methodological differences between studies.

First, the included studies used different processing pipelines to quantitatively determine functional and structural connectivity measures. Studies differed in the steps performed within the processing pipeline of resting-state fMRI data, which can influence the calculated correlation coefficient, such as global signal regression[61] and different nuisance regression schemes to remove confounds from the BOLD signal.[62] All included studies measured functional connectivity

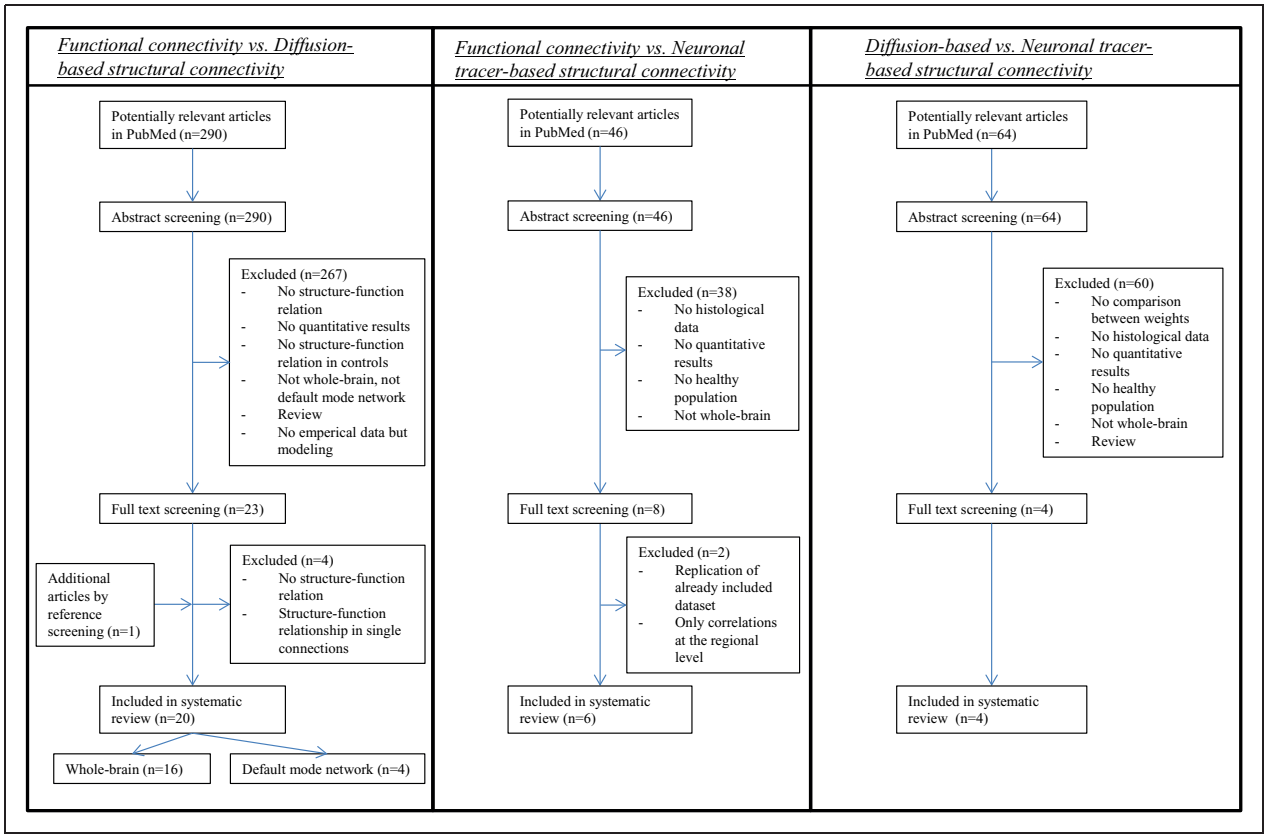

Figure 1. Flow chart showing the inclusion of studies evaluated for the three parts of our systematic review. Separate flow-chats are given for studies investigating the quantitative correlation between resting-state functional connectivity and diffusion-based structural connectivity measures, resting-state functional connectivity and neuronal tracer-based structural connectivity measures and diffusion-based and neuronal tracer-based structural connectivity measures.

strength as the correlation of low-frequency BOLD fluctuations. Most studies applied a Fisher's Z transformation to the correlation coefficient that is necessary for statistical analyses; some studies used the non-transformed correlation coefficient as functional connectivity strength. Diffusion-based structural connectivity can be determined by applying tractography algorithms to reconstruct white matter tracts in the brain. There are different algorithms to map diffusion-based structural connectivity as well as multiple parameters that affect the mapping of structural connections. Examples are the choice of diffusion model at the voxel level (e.g. tensor or higher-order), local or global tract modelling, deterministic or probabilistic tractography and the decision regarding which quantitative structural connectivity measure to use (e.g. number of streamlines or fractional anisotropy (FA) over streamlines). Different tractography algorithms and parameter settings will likely lead to different structural networks.[63] This may have influenced the calculated structure–function relationships. Most included studies used a streamline-based measure of structural connectivity strength, such as the connection density or streamline count. A minority of studies used measures of structural integrity (e.g. FA and even mean diffusivity (MD) over streamlines) as quantitative measures related to the features (i.e. axonal density or myelination of tracts) of anatomical substrates underlying functional connectivity.[50–52] Inferring quantitative connectivity strength from these integrity measures, however, remains controversial.[64] The FA is highly variable across the brain and may be low in voxels containing complex fiber orientations such as crossing and bending fibers. Furthermore, the FA, and other parameters such as MD, axial diffusivity and radial diffusivity, has shown to be confounded by the underlying white matter architecture and partial volume effects, all independent of the strength of these connections.[65,66]

Second, the spatial and angular resolution of the acquired diffusion-weighted data and temporal resolution of the resting-state fMRI data may influence its ability to resolve structural and functional connectivity, respectively. One study included in this review determined the structure–function relationship with state-of-the-art, high angular, spatial and temporal resolution MR data, as well with a lower resolution

Table 1. Resting-state functional connectivity and diffusion-based structural connectivity at whole-brain level.

First author	Year	Title	Journal	Species (n)	Age	Structural measure (diffusion)	Functional measure	Regions (n)	Cortical or subcortical	Inter- or intra-hemispheric	Correlation method	Correlation	p
Honey et al.[28]	2009	Predicting human resting-state functional connectivity from structural connectivity.	PNAS	Human (5)	29.4 ± 3.4 years	Connection density (number of connections per unit surface)	Pearson correlation	Low-resolution: 66 High-resolution: 998	Cortical	Both	Pairwise correlation	1) Low resolution, all connections: 0.66 2) Low resolution, removing absent/inconsistent connections: 0.82 3) High resolution, all connections: 0.36 4) High resolution, removing absent/inconsistent connections: 0.53	All $p < 0.001$
Skudlarski et al.[32]	2008	Measuring brain connectivity: diffusion tensor imaging validates resting state temporal correlations.	Neuro Image	Human (41)	28 ± 10 years	Weighted sum of connections; with penalizing more indirect pathways	Fisher's Z transformed correlation coefficient	5000		Both	Pearson r	0.18 ± 0.10 for individual subjects	$p < 0.00001$ for 39 out of 42 subjects
van den Heuvel et al.[40]	2015	The neonatal connectome during preterm brain development.	Cerebral Cortex	Human (27)	Between week 30 and week 42 of corrected gestational age	Number of streamlines (NOS)	Correlation between time series	56	Cortical + amygdala and hippocampus	Both	Pearson correlation	0.31 ± 0.089 (mean ± SD)	Not reported
Abdelnour et al.[41]	2014	Network diffusion accurately models the relationship between structural and functional brain connectivity networks.	Neuro Image	Human (8)	Adult	Weighted sum of tracts	Fisher's Z transformed correlations	90	Cortical	Both	Pearson correlation	0.23–0.27 for individual subjects; mean: r = 0.25.	Not reported
Horn et al.[8]	2014	The structural–functional connectome and the default mode network of the human brain.	Neuro Image	Human (19)	26.6 ± 2.98 years	Number or random walks (probabilistic tractography (Prob)) and Number of fibers (global tracking (Global))	Full and Partial correlation	40,000 voxels	Cortical	Both	Pearson correlation	1) Prob. Full: 0.046 ± 0.018 (0.02–0.08) 2) Global. Full 0.017 ± 0.010 (0.006–0.02) 3) Prob. Partial: 0.024 ± 0.029. 4) Global. Partial 0.015 ± 0.017. (Individual participants)	All $p < 0.001$
Sun et al.[42]	2014	Disrupted functional brain connectivity and its association to structural connectivity in amnestic mild cognitive impairment and Alzheimer's disease.	PLoS One	Human (14)	68.6 ± 8.36 years	Fiber numbers connecting each pair of brain regions	Fisher's Z transformed correlation coefficient	1024	Both	Both	Correlation coefficient	1) All connections: 0.37. 2) Excluding absent structural connections: 0.51.	Not reported

(continued)

Table 1. Continued

First author	Year	Title	Journal	Species (n)	Age	Structural measure (diffusion)	Functional measure	Regions (n)	Cortical or subcortical	Inter- or intra-hemispheric	Correlation method	Correlation	*p*
Hagmann et al.[36]	2008	Mapping the structural core of human cerebral cortex.	PLoS Biology	Human (5)	29.4 ± 3.4 years	Deterministic tractography; connection density (number of connections per unit surface)	Cross-correlation	66	Cortical	Both	Correlation (R^2)	0.62	$p < 10^{-10}$
Ding et al.[38]	2013	Altered functional and structural connectivity networks in psychogenic non-epileptic seizures.	PLoS One	Human (20)	21.85 ± 1.70 years	Connection density	Absolute functional connectivity strength; correlation coefficient	90	Both	Both	Pearson correlation	0.3213 ± 0.0525	Not reported
Hagmann et al.[37]	2010	White matter maturation reshapes structural connectivity in the late developing human brain.	PNAS	Human (30)	18 months – 18 years	Product between connection density & apparent diffusion coefficient (ADC)	Pearson correlation	66 and 241	Cortical	Both	Correlation coefficient	1) Young: low resolution: 0.30 2) Young: high resolution: 0.36 3) Old: low resolution: 0.43 4) Old: high resolution: 0.46	All $p < 0.001$
van den Heuvel et al.[39]	2013	Abnormal rich club organization and functional brain dynamics in schizophrenia	JAMA psychiatry	Human (45 and 51)	1) 28.9 ± 7.9 years 2) 30.2 ± 8.7 years	Streamline count	Correlation between time series	68 cortical and 68 + 14 subcortical	Cortical and both	Both	Correlation analysis	1) Cortical: 0.25 ± 0.048 (mean ± SD) 2) Whole brain: 0.19 ± 0.049 (mean ± SD) 3) Cortical: 0.25 ± 0.062 (mean ± SD) 4) Whole brain: 0.18 ± 0.051 (mean ± SD)	Not reported
Reid et al.[46]	2016	A cross-modal, cross-species comparison of connectivity measures in the primate brain.	Neuro Image	Human (174 and 96)	1) 10–80 years 2) 19–85 years	Probabilistic tractography: Streamline density (amount of tracts divided by distance and region size	Correlation between time series.	80	Cortical + hippocampus and amygdala	Both	Spearman rank correlation	1) 0.65 2) 0.49	Not reported
Zimmermann et al.[43]	2016	Structural architecture supports functional organization in the human brain at a region wise and network level.	Human brain mapping	Human (47)	18–80 years (mean ± SD: 41.49 ± 18.36)	Probabilistic fiber tracking: Number of voxels between a pair of regions, weighted to surface area and corrected for mean tract length	Fisher's Z transformed Pearson's correlation coefficient	68	Cortical	Both	Spearman's correlation.	1) Individual subjects: 0.19–0.36 2) Group mean: 0.27 ± 0.04 (mean ± SD)	1 and 2) $p<0.001$ for all subjects 3 and 4) Not reported
Fukushima et al.[45]	2017	Structure–function relationships during segregated and integrated network states of human brain functional connectivity.	Brain Structure and Function	Human (84)	22–36 years	Number of streamlines divided by geometric mean of surface areas	Fisher's Z transformed Pearson correlation coefficient	113	Cortical	Both	Pearson correlation coefficient	1) Integrated state: ~0.27 2) Segregated state: ~0.22 *(Estimated from graph)*	$p < 6.6 \times 10^{-24}$

(continued)

Table 1. Continued

First author	Year	Title	Journal	Species (n)	Age	Structural measure (diffusion)	Functional measure	Regions (n)	Cortical or subcortical	Inter- or intra-hemispheric	Correlation method	Correlation	*p*
Wirsich et al.[44]	2016	Whole-brain analytic measures of network communication reveal increased structure–function correlation in right temporal lobe epilepsy.	Neuro Image: Clinical	Human (13)	20–59 years (mean: 31.8 years)	Number of streamlines (log)	Pearson correlation between time series	512	Both	Both	Pearson correlation	1) 0.375	$p < 10^{-6}$
Goñi et al.[48]	2014	Resting-brain functional connectivity predicted by analytic measures of network communication.	PNAS	Human (5 and 40 and 25)	1) 29.4 ± 3.4 year 2) 25.3 ± 4.9 years 3) 29.4 ± 7.7 years	Fiber density	Pearson cross-correlations	1) 66 2) ~1000	Cortical	Both	Correlation	1) Average all 3 datasets: r = 0.515. 2) Average all 3 datasets: r = 0.338.	$p < 0.001$
Collin et al.[47]	2017	Affected anatomical rich club and structural–functional coupling in young offspring of schizophrenia and bipolar disorder patients.	Biological Psychiatry	Human (39)	12.7 ± 2.2 years	Number of streamlines rescaled to a Gaussian distribution	Pearson correlation	114	Cortical	Both	Correlation analysis	r = 0.25 ± 0.05 (mean ± SD) *(Estimated from graph)*	Not reported

Note: Numbers before the correlation values are corresponding to the numbers in Figure 2. SD: standard deviation.[8,28,32,36–48]

Table 2. Resting-state functional connectivity and diffusion-based structural connectivity in the default mode network.

First author	Year	Title	Journal	Species (*n*)/ Anesthesia	Age	Structural measure (diffusion)	Functional measure	Regions (n)	Cortical or subcortical	Inter- or intra-hemispheric	Correlation method	Correlation	*p*
Sun et al.[49]	2017	Modular-level alterations of structure–function coupling in schizophrenia connectome.	Human brain mapping	Human (20)	37.8 ± 8.8 years	Streamline density.	Fisher's Z transformation of correlation coefficient	24 out of 66 and 235 out of 1024	Cortical	Both	Correlation analysis	1) Low resolution: 0.336 ± 0.014 (mean ± SE) 2) High resolution: 0.124 ± 0.006 (mean ± SE)	Not reported.
Khalsa et al.[50]	2014	The structural and functional connectivity of the posterior cingulate cortex: Comparison between deterministic and probabilistic tractography for the investigation of structure–function relationships.	Neuro image	Human (15)	24.6 (23–29)	Deterministic: FA; Probabilistic: number of tracts that reached the target from seed	Correlation coefficient	4	Cortical	Both	Bivariate correlation analysis	1) Streamline tractography: 0.48 2) Probabilistic tractography: 0.33	1) $p = 0.005$; 2) $p = 0.027$
Hübner et al.[51]	2017	The connectomics of brain demyelination: Functional and structural patterns in the cuprizone mouse model.	Neuro image	Mice (8) / Medetomidine (bolus 0.3 mg/kg + continuous subcutaneous infusion of 0.6 mg/kg).	20 weeks	FA	Partial correlation	8	Both	Both	Pearson r	0.14	$p < 0.001$
Tsang et al.[52]	2017	White matter structural connectivity is not related to cortical resting-state functional connectivity over the healthy adult lifespan.	Frontiers in Aging Neuro science	Human (177)	18–87	Deterministic: FA, MD, tract length and number of streamlines	Fisher's Z transformation of Pearson correlation coefficient	6	Cortical	Both	Pearson correlation (r)	1) FA: 0.14; 2) MD: −0.15 3) Tract length: 0.12; 4) Number of streamlines: 0.14	1) $p = 0.595$ 2) $p = 0.359$ 3) $p = 0.778$ 4) $p = 0.513$

Note: Numbers before the correlation values are corresponding to the numbers in the forest plot in Figure 3. For resting-state functional MRI studies in animals, the applied anesthesia regime is mentioned under Species (n)/ Anesthesia. SE; standard error; FA: fractional anisotropy; MD: mean diffusivity.[49–52]

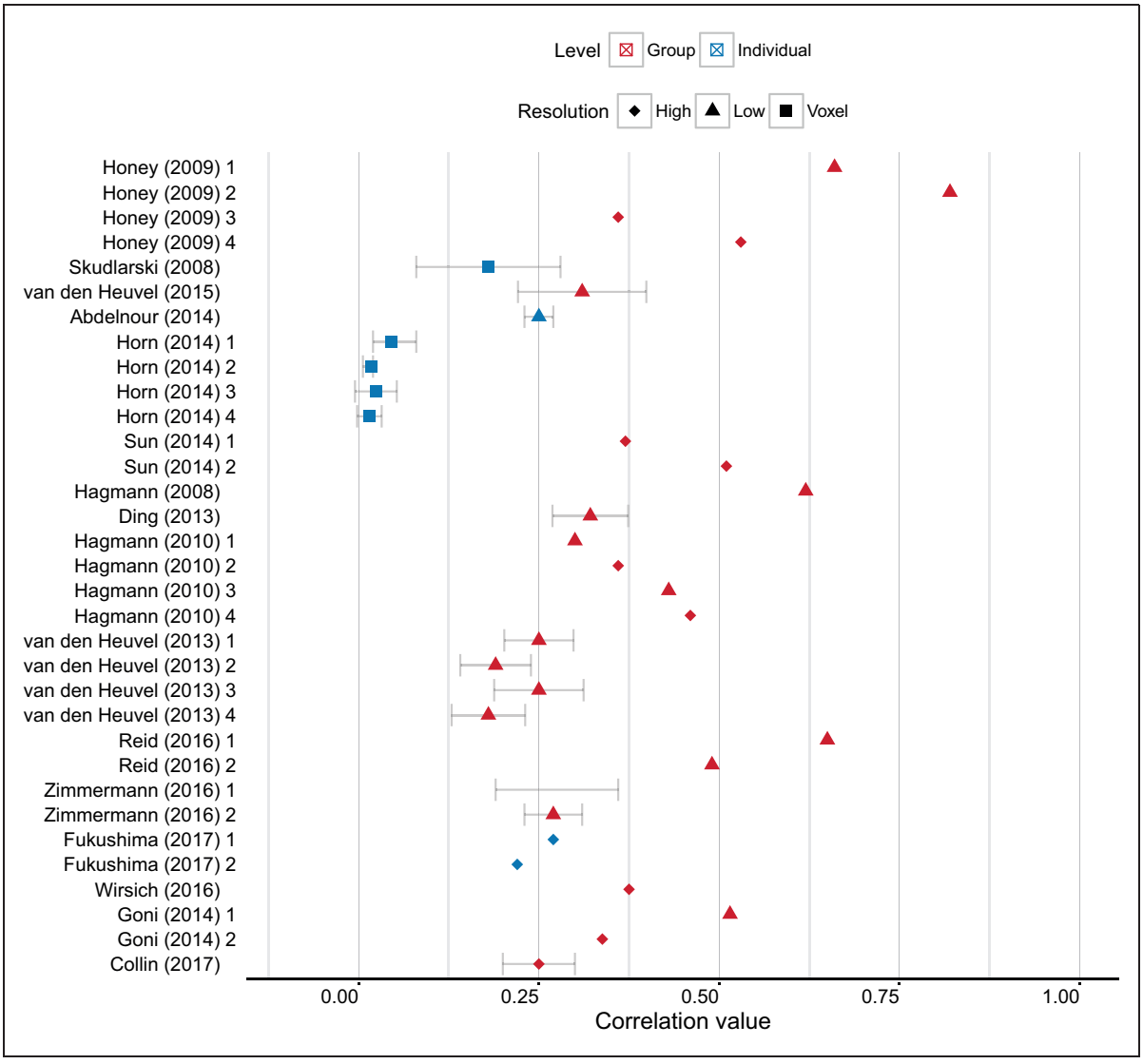

Figure 2. Reported correlations between quantitative resting-state functional connectivity and diffusion-based structural connectivity measures at the whole-brain level. Network comparisons were done at single voxel level or with regions of interest, where inclusion of >100 regions was considered as high-resolution and <100 regions as low resolution. The group correlation values were averaged over groups, whereas the individual correlation values were derived from single subjects. The publication labels are extended with the corresponding numbers in Table 1. Error bars represent the range of individual subjects,[8,32,41,43] standard deviation[39,40,43,47] or unknown variation measures.[8,28,32,36–48]

dataset.[46] Higher structure–function correspondence was found with higher resolution data. The authors attribute this to an increased ability to resolve complex fiber architectures in diffusion-weighted data due to higher spatial and angular resolution, and a more temporally precise analysis of functional connectivity strength due to higher temporal resolution. These results suggest that different temporal and spatial resolutions across MR acquisitions in included studies may have influenced the reported structure–function correlation.

Third, at the analysis level, there were differences in individual versus group level comparisons and in voxel versus regional level comparisons. Group and regional level comparisons resulted in higher structure–function relationships compared to individual and voxel level analyses, respectively. Group level analysis in which time-series and diffusion-weighted tract reconstructions are averaged across individuals or animals reduces the influence of inter-subject variability. Furthermore, averaging voxel data across larger regions boosts the connectivities' signal-to-noise ratio. Reduced inter-subject variability and increased signal-to-noise might reduce the variation in correlation values. We have not explicitly tested this as the number of included studies was too small to determine the effect of covariates accurately.

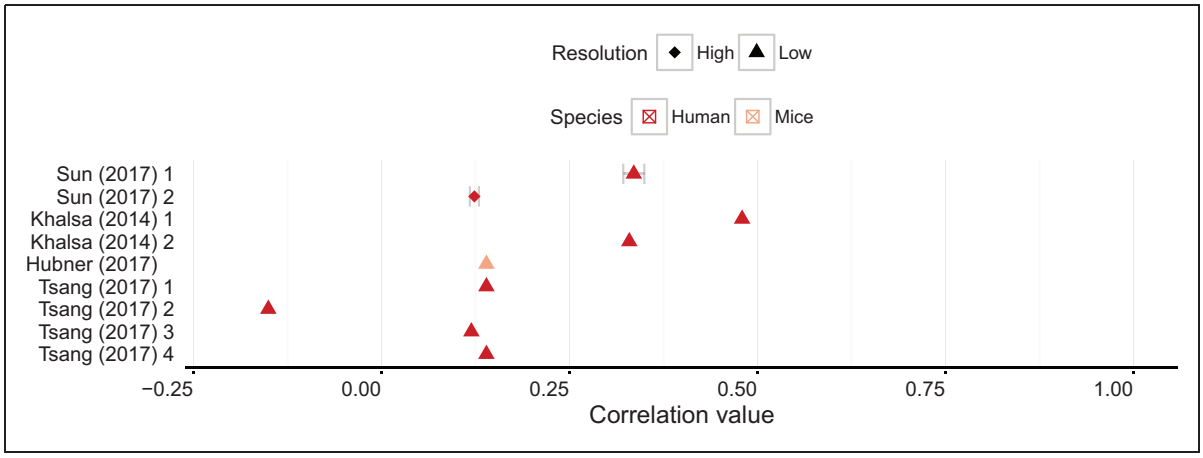

Figure 3. Reported correlations between quantitative resting-state functional connectivity and diffusion-based structural connectivity measures in the default mode network. Studies were performed at two resolution levels, in which inclusion of >100 regions was considered as high-resolution and <100 regions as low resolution. The publication labels are extended with the corresponding numbers in Table 2. Error bars represent the standard error of the mean.[49–52]

Fourth, for the regional analyses, the choice of atlas parcellation and region inclusion could influence the structure–function correlation value. Different atlases with different parcellation schemes[a] are available to divide the brain into regions, which can be used to define inter-regional structural and functional connectivity. The studies included in this review used a variety of atlases, which resulted in variable numbers of brain regions. Some studies included both a high and low-resolution parcellation (resulting in more and less included regions), and demonstrated higher structure–function relationships using a low-resolution parcellation.[28,37,49] The parcellation scheme chosen may influence quantitative measures of structural and functional connectivity[67] and possibly also their mutual relationship. A parcellation scheme may include only cortical structures, or may include both cortical and subcortical structures. Structure–function correlations have mostly been determined in cortical regions to exclude indirect connections via subcortical structures. Despite the suggestion given in a previous review to include subcortical structures to obtain a more complete and realistic picture of the brain's structure–function relationship,[23] only a few recent studies did so.[38,39,42,44,51] The results of one study indicate that the structure–function correlation may be slightly lower when including both cortical and subcortical regions ($r = 0.19$) compared to including cortical regions only ($r = 0.25$).[39] This lower correlation value might be caused by difficulties measuring signals from deeper brain structures at standard field strengths with surface coils[68] or by the highly specialized organization of subcortical structures with multiple parts connecting to various cortical regions.[69]

Lastly, the relatively high variance between studies may also be related to the dynamic nature of resting-state functional connectivity. All studies used stationary approaches to calculate functional connectivity, while functional networks can be considered as dynamic entities that change their topology on both long and short time-scales. One included study used a sliding window approach to determine dynamic functional connectivity, but used the median value (i.e. a stationary measure) to correlate functional connectivity to diffusion-based structural connectivity.[45] Directions and strengths of functional connections can change within seconds to minutes during the acquisition of resting-state fMRI scans.[70] There is ample evidence that these network dynamics cannot be attributed to noise: they are intrinsic brain properties with a neural origin.[71] Recently, varying correlations between structural connectivity and dynamic functional connectivity have been demonstrated in macaques, with higher correlations using longer time windows.[54] How the relatively stable structural network would drive dynamics in functional connectivity remains an unanswered question.[26]

To what extent is functional connectivity strength correlated to neuronal tracer-based structural connectivity strength?

A smaller number of studies investigated the quantitative relationship between functional connectivity and neuronal tracer-based structural connectivity. An overview of all extracted data from the included studies is given in Table 3. Included studies were performed in humans,[46,53] macaques,[34,53,55] mice[11] and rats.[56] The two studies on human subjects compared resting-state functional connectivity strength in humans with neuronal tracer-based structural connectivity strength in

Table 3. Resting-state functional connectivity and neuronal tracer-based structural connectivity.

First author	Year	Title	Journal	Species (n)/ Anesthesia	Age	Structural measure (neuronal tracer)	Functional measure	Regions (n)	Cortical or subcortical	Inter- or intra-hemispheric	Correlation method	Correlation	p
Stafford et al.[11]	2014	Large-scale topology and the default mode network in the mouse connectome.	PNAS	Mice (9) / 1–1.5% isoflurane	Adult	Connection density: strength/volume of target: Average of 2 directions	Fisher's Z transformed correlation	168	Cortical	Both	Pearson correlation	0.24	$p = 1.4136 \times 10^{-61}$
Miranda-Dominguez et al.[11]	2014	Bridging the gap between the human and Macaque connectome: a quantitative comparison of global interspecies structure–function relationships and network topology.	The Journal of Neuro science	Human (26) & Macaque (11) / <1% isoflurane.	Human: 26 ± 4 years Macaque: 5 ± 0.4 years	Number of neurons in source regions (retrograde)/total labelled neurons in the brain minus the injected area	Cross-correlation of time series	29	Cortical	Intra-hemispheric	Regression	1) Macaque: 0.34 (without whole brain regression 2) Macaque: 0.35 (with whole brain regression) 3) Human: 0.38 (without whole brain regression) 4) Human: 0.42 (with whole brain regression)	All $p < 1 \times 10^{-12}$
Shen et al.[34]	2012	Information processing architecture of functionally defined clusters in the macaque cortex.	The Journal of Neuro science	Macaque (6) / 1% isoflurane.		Strength is relative to other brain sites labelled by the same injection	Pearson correlation of time series	82	Cortical + hippocampus and amygdala	Both	Cosine similarity	1) 0.32. 2) intra-hemispheric: 0.34 (left: 0.34; right 0.33) 3) inter-hemispheric: 0.24 (left: 0.25; right 0.23)	Not reported
Grayson et al.[55]	2016	The rhesus monkey connectome predicts disrupted functional networks resulting from pharmacogenetic inactivation of the amygdala.	Neuron	Macaque (4) / 1.3–1.7% isoflurane.	Adult	Communicability metric (G); weighted sum: 1) TTX: continuous and exponentially distributed 2) TTU; 0,1,2,3	Pearson correlation of time series	80	Cortical + amygdala	Both	Correlation	Amydala-cortical: 1) TTX: 0.737 (CI:0.55–0.854) 2) TTU: 0.613 (CI:0.369–0.778) Corticocortical: 3) TTX: 0.6 (CI:0.552–0.645) 4) TTU: 0.523 (CI:0.469–0.574)	1) $p < 10^{-6}$ 2) $p < 10^{-4}$ 3) $p < 10^{-6}$ 4) $p < 10^{-6}$
Reid et al.[46]	2016	A cross-modal, cross-species comparison of connectivity measures in the primate brain.	Neuro Image	Human (174 and 96)	1) 10–80 years 2) 19–85 years	Tracer density (0–3)	Correlation between time series	80	Cortical + hippocampus and amygdala	Both	Spearman rank correlation	1) 0.30 2) 0.22	Not reported
Díaz-Parra et al.[56]	2017	Structural and functional, empirical and modelled connectivity in the cerebral cortex of the rat	Neuro Image	Rat (14) / Urethane (1.2 g/kg).		Qualitative strengths (0 (not-present) – 7 (very strong)	Fisher's z transformed correlation coefficient	32	Cortical + hippocampus and amygdala	Intra-hemispheric (ROIs left and right combined)	Spearman correlation	1) 0.48 (Present & non-present connections) 2) 0.48 (Only present connections) 3) Correcting for distance; 0.35 (Present and non-present connections) 4) Correcting for distance: 0.33 (Only present connections)	1) $p < 2 \times 10^{-29}$ 2) $p < 2 \times 10^{-19}$ 3) $p < 3 \times 10^{-15}$ 4) $p < 2 \times 10^{-9}$

Note: Numbers before the correlation values are corresponding to the numbers in the forest plot in Figure 4. For functional resting-state MRI studies in animals, the anesthesia regime is mentioned under Species (n)/Anesthesia. CI: 95% confidence interval. TTU: unenhanced tract tracer matrix, TTX: enhanced tract tracer matrix (more continuous and exponentially distributed).[11,34,46,53,55,56]

macaques.[46,53] All studies report a positive correlation between functional connectivity strength and neuronal tracer-based structural connectivity strength (Figure 4). The reported structure–function correlation coefficients between functional and neuronal tracer-based structural connectivity strength were highly variable between studies. The range of reported values is comparable to the reported correlation values between functional and diffusion-based structural connectivity strength.

The variation in correlation values between functional connectivity and neuronal tracer-based structural connectivity may be caused by similar methodological differences between studies as described above for the correlation between functional and diffusion-based structural connectivity strength. Besides the already described methodological differences, there are some additional factors that may have influenced the relationship between functional and neuronal tracer-based structural connectivity strength.

First, since many of the studies comparing functional connectivity with neuronal tracer-based structural connectivity are performed in animals, the use of anesthesia during resting-state fMRI acquisition may have influenced the reported structure–function relationship. Functional connectivity varies under different anesthesia protocols.[72] The studies included in this review used different anesthesia protocols (Table 3), which may have attributed to the variation in the relationship between functional and neuronal tracer-based structural connectivity.

Second, the relationship between functional and neuronal-tracer based structural connectivity is determined in different species, including macaques, mice and rats. A relatively low structure–function correlation was found in mice, which may be caused by the difficulties with performing resting-state fMRI acquisitions in small rodents,[73] by smaller voxel sizes which may introduce more variation, or by differences in brain organization across species. Although the macaque and human brain have comparable structure–function relationships,[53] the comparison between the rodent and human brain is less clear. Larger sized brains (such as the human or macaque brain) contain higher percentages of white matter compared to smaller rodent brains,[74] which may influence structural network constructions. On the other hand, functional networks in the rodent and human brain are organized in a similar way.[75] Recently, interest has been raised in comparing organizational and topological aspects of brain networks across different species, named comparative connectomics.[76] The authors of this review propose the idea that brains of different species share common features, but also have subtle variations that enable species-specific behavior. More structure–function research across different species is needed to identify whether inter-species variability in structure–function correlations is due to species-specific organization of structural and functional networks or due to methodological differences.

Lastly, neuronal tracer-based structural connectivity strength is usually taken from an available database, like the CoComac database[77] or the Allen Mouse Brain Connectivity Atlas (http://connectivity.brain-map.org).[78] Neuronal tracer-based structural connectivity strength can be determined by quantifying the fluorescence pattern and intensity in the projection areas of the region of interest. However, a recent study showed that the amount of tracer injected in the region of interest influences the relationship between functional and neuronal tracer-based structural connectivity strength.[79] This study suggests that neuronal tracer-based structural connectivity strength should be corrected for the amount of tracer injected, a factor that is often neglected.

To what extent is diffusion-based structural connectivity strength correlated to neuronal tracer-based structural connectivity strength?

The correlation values between functional connectivity and structural connectivity measured with diffusion-weighted imaging or neuronal tracers overlap, despite clear methodological differences between these techniques measuring structural connectivity. Diffusion-based tractography maps structural connectivity probabilistically at the macro-scale level and does not provide directional information. Although it has been suggested that tract reconstructions include polysynaptic connections, its macroscopic resolution does not allow information about these microstructural properties.[35] In comparison, neuronal tracers map structural connectivity deterministically at both the micro- and mesoscale level of axonal projections. It provides directional information through anterograde and retrograde labelling and can distinguish monosynaptic and polysynaptic connections. Therefore, we also investigated the relationship between diffusion-based and neuronal tracer-based structural connectivity. The extracted data from the included studies on this comparison are given in Table 4. These studies were performed in macaques,[58,59] a vervet monkey[58] and mice.[57] One study compared diffusion-based structural connectivity strength in humans with neuronal tracer-based structural connectivity strength in macaques.[46]

The included studies report a moderate correspondence between diffusion-based and neuronal tracer-based structural connectivity strength (Figure 5). Although diffusion-weighted imaging is currently the only way to determine white matter structural connectivity in vivo, it does so in an indirect way by

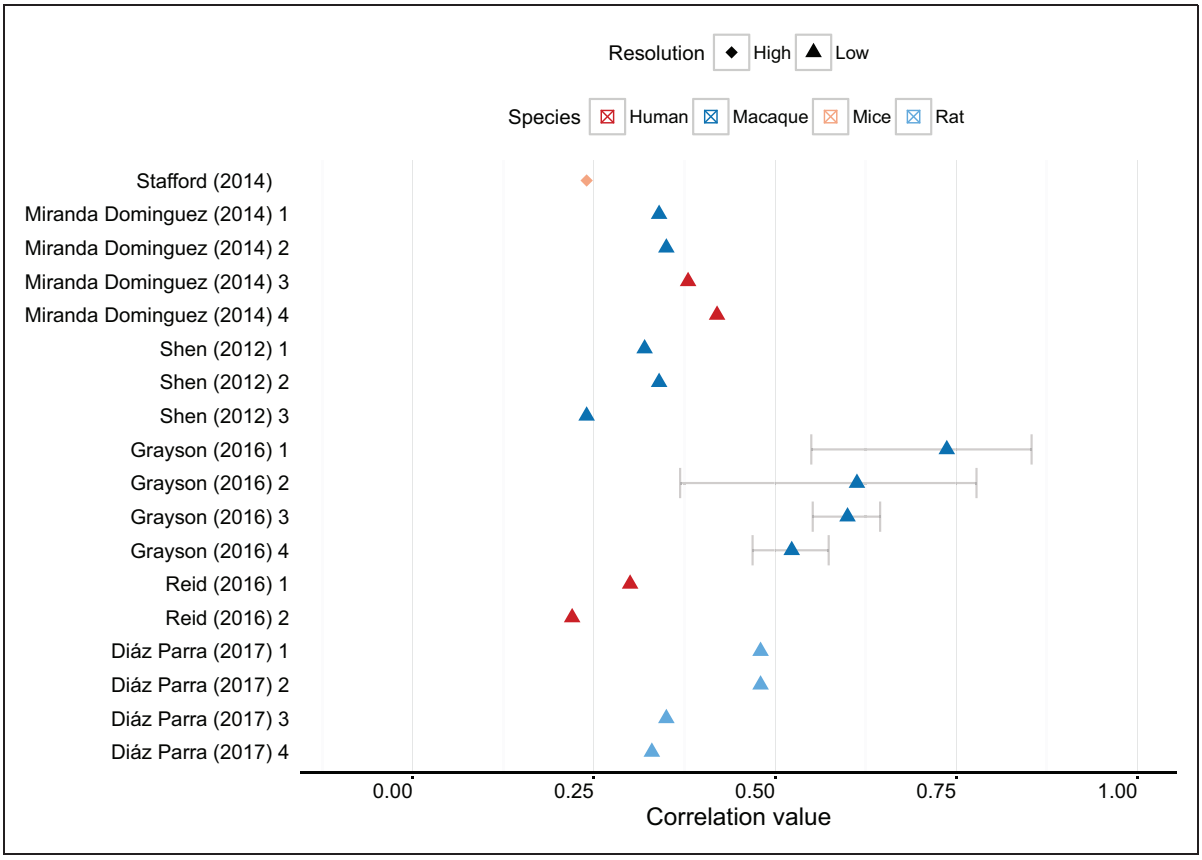

Figure 4. Reported correlations between quantitative resting-state functional connectivity and neuronal tracer-based structural connectivity measures. Studies were performed at two resolution levels, in which inclusion of >100 regions was considered as high-resolution and <100 regions as low resolution. Studies involved four different species. The publication labels are extended with the corresponding numbers in Table 3. Error bars represent the 95% confidence interval.[11,34,46,53,55,56]

inferring the direction and trajectory of white matter tracts from the diffusion of water.[16,80] Recent research has demonstrated that these tractography-based structural networks do not always reflect the axonal projections between regions measured with neuronal tracers,[18] and are especially limited in reconstructing long-distance connections.[81] In line with this, structural networks based on diffusion-tractography are affected by many false positives,[19] possibly because of the limited ability to resolve crossing fibers at sub-voxel level. In addition, the applied tractography algorithm and parameter settings affect the reconstructed structural networks,[63] which may also influence the correspondence to neuronal tracer-based structural networks. On the other hand, the correspondence between diffusion-based and neuronal tracer-based tracts (and networks) may be affected by histological procedures as well (e.g. variations in site of tracer injection, the used tracing method, processing and registration of images, and regions of interest). However, neuronal-tracers are still regarded as the 'gold standard' way to map anatomical connections. Several studies have tried to identify the tractography method that best matches the 'gold standard' neuronal tracer-based structural network,[82] as well as to improve tractography methods, e.g. by using machine-learning techniques,[83] imposing anatomical priors and constraints[84,85] or applying filtering methods.[86–88] Higher resolution diffusion-weighted data, such as the data acquired in the Human Connectome project,[89] may help to resolve more complex fiber configurations (e.g. crossing, bending or fanning) and to determine a more accurate diffusion-based structural network.

New insights and implications

We report a robust positive correlation between functional connectivity and structural connectivity, which supports the hypothesis that structural network connectivity, at least partially, shapes functional network connectivity,[23,60] also on a quantitative level. We also showed that the reported structure–function correlation is highly variable across studies, and identified many methodological differences between studies that may have contributed to this large variation. This methodological heterogeneity complicated the comparison

Table 4. Diffusion-based structural connectivity and neuronal tracer-based structural connectivity.

First author	Year	Title	Journal	Species (n)	Age	Structural measure (diffusion)	Structural measure (neuronal tracer)	Regions (n)	Cortical or subcortical	Inter- or intra-hemispheric	Correlation method	Correlation	*p*
Calabrese et al.[57]	2015	A diffusion MRI tractography connectome of the mouse brain and comparison with neuronal tracer data.	Cerebral Cortex	Mice (2)	Adult	Probabilistic; sum of fibers, normalized by the volume of the seed region	Total volume of pixels in target, normalized by injection site volume; log transformed	469	Both	Both	Spearman-rank	0.42	$p < 0.05$
Donahue et al.[58]	2016	Using diffusion tractography to predict cortical connection strength and distance: A quantitative comparison with tracers in the monkey	The Journal of Neuro science	Macaque (1) and Vervet (1; scanned twice)	Adult	Probabilistic: Number of streamlines	Fraction of labeled neurons in source/total labeled neurons extrinsic to injected area	29	Cortical	Intrahemispheric	Pearson correlation	1) Macaque: 0.59 2) Vervet: 0.60 3) Vervet: 0.55	Not reported
van den Heuvel et al.[40]	2015	Comparison of diffusion tractography and tract-tracing measures of connectivity strength in rhesus macaque connectome.	Human Brain mapping	Macaque (10)	Adult	Deterministic: 1) Number of streamlines (NOS) 2) Streamline density	Level of tracer density/strength: 1(weak), 2 (intermediate), 3(strong). (2 datasets: CoCoMac and Markov-Kennedy)	39 (CoCo Mac) and 29 (Markov)	Cortical	Intrahemispheric	Correlation	1) NOS: 0.25 (CoCoMac) 2) NOS: 0.26 (Markov) 3) Streamline density: 0.31 (CoCoMac) 4) Streamline density: 0.30 (Markov)	1) $p = 0.002$ 2) $p < 0.001$ 3) $p < 0.001$ 4) $p < 0.001$
Reid et al.[46]	2016	A cross-modal, cross-species comparison of connectivity measures in the primate brain	Neuro Image	Human (174 and 96)	1) 10–80 years 2) 19–85 years	Probabilistic tractography: Streamline density (amount of tracts divided by distance and region size)	Tracer density (0–3)	80	Cortical + hippocampus and amygdala	Both	Spearman rank correlation	1) 0.41 2) 0.47	Not reported

Note: Numbers before the correlation values are corresponding to the numbers in the forest plot in Figure 5.[46,57–59]

between studies, and stresses the need for validation and standardization in this research field. To enable comparisons across studies, a consensus should be reached about the methodological pipeline (e.g. (pre-)processing steps) as well as on how to determine nodes, edges and strength of edges in structural and functional networks. We recommend future studies to use a Fisher's Z-transformed correlation coefficient as a measure of functional connectivity strength to enable comparison across studies, and to include subcortical structures to completely identify the whole brain structure–function relationship. In addition, when determining structural networks, future studies should use a diffusion-based tractography method that best fits with the acquired data and most accurately reflects neuronal tracer data.

Nevertheless, despite all improvement made over the years, diffusion-based tractography remains an indirect way of inferring white matter structural connectivity in the brain, which has shown to generate considerable amounts of false positive and false negative connections.[18,19,57,82,90] Furthermore, diffusion-based tractography has limited ability to solve intra-cortical connections because of the relatively low anisotropy, thereby biasing results towards white matter connections. The moderate correlation between diffusion-based and neuronal tracer-based structural connectivity shows that the diffusion-based structural network does not accurately reflect all axonal connections. To evaluate the differences between both techniques in relation to functional connectivity, we also included recent studies that correlated functional connectivity strength with structural connectivity strength measured in a more direct way with neuronal tract tracers in animals. These studies showed a comparable positive structure–function relationship, which overlapped with the range of correlation values between functional connectivity and diffusion-based structural connectivity strength. However, one included study compared two human functional datasets with human diffusion-based and macaque neuronal tracer-based structural connectivity,[46] and demonstrated lower correlation values with neuronal tracer-based structural connectivity than with diffusion-based structural connectivity. Although humans and macaques show comparable structure–function correlations,[53] this lower correlation value of human functional connectivity strength with macaque neuronal tracer-based connectivity strength can also be explained by differences between species. Therefore, whether the structure–function relationship differs across distinct structural connectivity

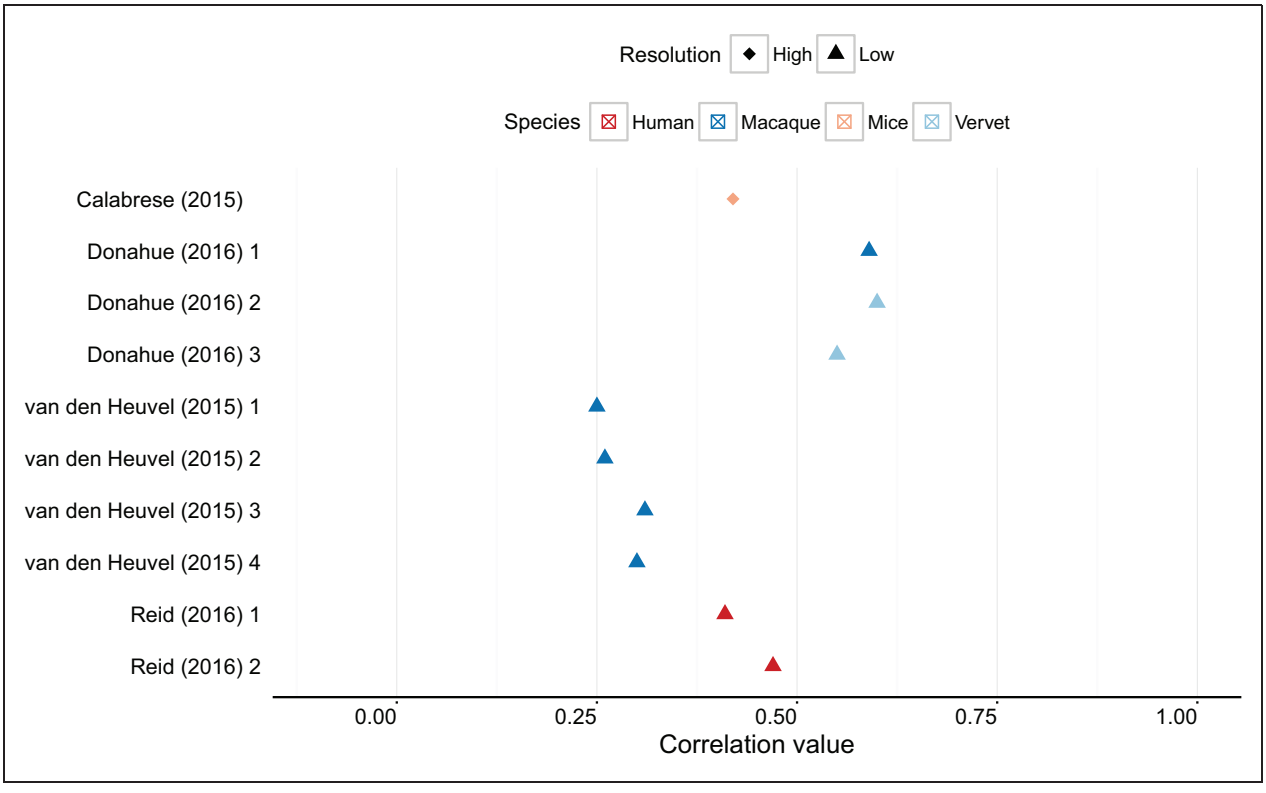

Figure 5. Reported correlations between diffusion-based and neuronal tracer-based structural connectivity strength. Studies were performed at two resolution levels, in which inclusion of >100 regions was considered as high-resolution and <100 regions as low resolution. Studies involved four different species. The publication labels are extended with the corresponding numbers in Table 4.[46,57–59]

reconstruction techniques remains an open question. Investigating functional, diffusion- and neuronal tracer-based structural connectivity in the same species would be of great interest for further exploration of the structure–function relationship on different hierarchical levels.

Future prospects

Although our review shows that there is a robust positive structure–function relationship in the brain, this relationship is complex in nature. Strong inter-regional functional connectivity co-exists with weak direct structural connectivity between the same regions. This supports the hypothesis that indirect structural connections also play an important role in the existence of functional connectivity.[33] However, these indirect connections are often not taken into account. Future studies could consider indirect connections in at least two different ways. First, based on neuronal tracer data that provide directional information on the underlying axonal projections. By using this directional information, it has been shown that functional connectivity without direct structural connections is generated by network-level properties rather than by signals flowing through a third area.[91] The metric source information provides a quantitative measure for structural connectivity that is corrected for pathways that are branching off the shortest pathway between two regions and forming indirect connections.[48] Second, another way to tackle the influence of indirect connections is by inferring directionality of functional connections from resting-state fMRI data itself. This could be done with network methods based on effective connectivity.[92] Calculating effective connectivity typically requires an a priori specification of network nodes and expected edges. More liberal methods are the conditional Granger causality, dynamic causal modelling and the transfer entropy methods.[93–95] For example, with conditional Granger causality, only direct connections are captured (e.g. region A directly connecting to region C), and indirect connections (region A connecting to region B, which connects to region C) are excluded by means of regression with signals in other network regions (in this example the signal in region B). Effective connectivity strengths affect the quantification of structure–function relationship in the brain.[96] We have not included effective connectivity network studies in our assessment, as between-study comparability would become even more complicated given the variations in the a priori model specifications.

Despite the robust positive structure–function relationship, we found a high variability in the reported structure–function relationship, which may be caused by the methodological differences across studies. A considerable part of the variation may be explained by the use of different atlases as well as by different regions of interest and connections included in the analyses. It might be that different regions, but also different types of connections exhibit distinct structure–function relationships. Identification of brain areas where structural and functional networks overlap (and deviate) may guide future research, i.e. whether applying a combined approach may be more beneficial than either technique alone. Inter-hemispheric functional connections between homotopic regions are often stronger than intra-hemispheric connections or inter-hemispheric connections between non-homotopic regions.[97] Two of the included studies showed a slightly higher structure–function relationship for intra-hemispheric connections compared to inter-hemispheric connections,[34,47] possibly because of sparse inter-hemispheric structural connectivity. In addition, two studies investigated the structure–function relationship at the single region level.[43,79] They both showed a large range of structure–function relationships for connections between different regions, with correlations between -0.40 and 0.66[43] and between -0.2 and 0.7.[79] Future research should investigate the structure–function relationship for specific connections or regions, which may lead to more insights into pathway- and circuit-specific aspects of structure–function relationships in the brain.

The reported structure–function relationships, based on diffusion-based tractography or neuronal tracers, show similar variability and overlapping ranges. Nevertheless, one study showed that structure–function relationships differ when measuring structural connectivity strength on distinct hierarchical levels (i.e. macro-scale diffusion-based or meso-scale neuronal tracer-based structural connectivity). Future research on the structure–function relationship should ideally determine all connectivity measures on different hierarchical levels within the same species. To that aim, rodents may be appropriate, since detailed and robust comparisons are possible given the availability of multi-level structural connectivity databases, such as NeuroVIISAS[98] and the Allen brain atlas.[78] Resting-state fMRI in small animals is more difficult.[73] This is reflected by the relative low structure–function correlations found in mice.[11,51] More sophisticated protocols and pipelines have been proposed and developed to obtain reliable and noise-free functional datasets in small animals.[99,100] Despite these methodological challenges, understanding the structure–function relationship in small animals on different hierarchical levels is very important, since many disease models are currently investigated in rodents.[101] Rodents provide unique opportunities to investigate and map structure–function relationships in specific neuronal sub-circuits, for example with optogenetics[102] or

chemogenetics.[103] Moreover, animal research provides the opportunity to conduct controlled experiments and post-mortem investigation in a laboratory setting, both important to elucidate the underlying properties and mechanisms of structural and functional connectivity.

Lastly, we suggest researchers to share their structural and functional datasets. Increased availability of open source data of both structural and functional networks across different species enables large-scale inter-species analysis of structure–function relationships. The large variation in structure–function relationships reported in this review may partly be caused by small sample sizes and consequent low signal-to-noise in individual studies. This may be solved by combining datasets. From the included studies, it is clear that structural connectivity partly shapes functional connectivity, but the strength of the correlation is still unclear. Therefore, combining datasets and averaging structural and functional connectivity over a large number of individuals may reveal to what extent the structural network strength constrains, maintains and regulates the functional network strength. Excellent platform examples are Open Science Framework (https://osf.io/) and OpenNeuro (https://openneuro.org/).

Conclusion

In conclusion, this systematic review shows that functional and structural connectivity strength in the mammalian brain correlate positively, both at the macro-scale with diffusion-based structural connectivity and at the meso-scale with neuronal tracer-based structural connectivity. We think that methodological heterogeneity across included studies drives the substantial variability in reported correlation values. The exact quantitative relationship between structural and functional connectivity still needs to be elucidated. Methodological differences between studies complicate inter-study comparisons and stress the need for validation and standardization of structure–function analyses across studies. In addition, different network resolutions, brain subsystems and connectivity measures may expose distinct structure–function relationships, which emphasize the need to assess functional and structural connectivity at multiple scales.

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Note

a. Multiple examples are available at https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases.

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