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

Milou Straathof¹, Michel RT Sinke¹, Rick M Dijkhuizen¹ and Willem M Otte¹,²; 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

¹Biomedical MR Imaging and Spectroscopy Group, Center for Image Sciences, University Medical Center Utrecht and Utrecht University, Utrecht, the Netherlands
²Department 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.\textsuperscript{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.\textsuperscript{3} Brain regions with patterns of correlated fluctuations in the time-domain are considered functionally connected.\textsuperscript{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,\textsuperscript{5,6} such as the default mode network.\textsuperscript{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,\textsuperscript{9} of which an equivalent network has been demonstrated in non-human primates\textsuperscript{9} and rodents.\textsuperscript{10,11} Disturbances in this network are linked to multiple brain disorders, including Alzheimer’s disease, autism, schizophrenia, depression, chronic pain and others.\textsuperscript{12} Interestingly, regions within the default mode network which are functionally firmly connected, do not always have strong direct structural connections.\textsuperscript{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.\textsuperscript{15} Tractography reconstructs the white matter fiber geometry across the brain by propagating streamlines based on the water diffusion preference.\textsuperscript{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.\textsuperscript{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.\textsuperscript{18,19} In animals, structural connectivity can also be measured invasively with the use of neuronal tracers.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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. 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. In addition, removing the corpus callosum in monkeys reduced interhemispheric functional connectivity, but not when other smaller interhemispheric structural connections were still intact. 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. However, 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. 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. Similar positive correspondences have been reported in the comparison of functional networks with neuronal tracer networks. 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. 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]).
brain network resolution and correlation 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...
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.60–62

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

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**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.
| First author       | Year | Title                                                                 | Journal     | Species | Age               | Structural measure (diffusion) | Functional measure | Regions (n) | Cortical or subcortical | Inter- or intra-hemispheric | Correlation method | Correlation coefficient | Correlation | p         |
|-------------------|------|----------------------------------------------------------------------|-------------|---------|-------------------|--------------------------------|-------------------|-------------|------------------------|--------------------------|--------------------------|---------------------------|-------------|----------|
| Honey et al. 28   | 2009 | Predicting human resting-state functional connectivity from structural connectivity. | PNAS        | Human   | 29.4 ± 3.4 years | Connection density (number of connections per unit surface) | Pearson correlation | Low-resolution: 66 | Cortical | Both | Pairwise correlation | 1) Low resolution, all connections: 0.66 |
|                   |      |                                                                      |             |         |                   |                                |                   | High-resolution: 998 |          |                  |                        | 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 |
| Skudlarski et al. 32 | 2008 | Measuring brain connectivity: diffusion tensor imaging validates resting state temporal correlations. | Neuro Image | Human   | 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   | 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   | 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   | 26.6 ± 2.98 years | Number or random walks (probabilistic tractography (Probb)) 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 (0.01-0.08) | All p < 0.001 |
|                   |      |                                                                      |             |         |                   |                                |                   |                         |          |                  |                        | 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) |
| 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   | 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)
| First author          | Year | Title                                                                 | Journal                  | Species (n) | Age               | Structural measure (diffusion)                                                                 | Functional measure | Regions (r) | 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 | Diffusion: number of connections per unit surface | Cross-correlation | 66          | Cortical               | Both                           | Correlation (R²) | 0.62                 | p < 10⁻¹⁰          |
| Ding et al. 38       | 2013 | Altered functional and structural connectivity networks in psychoge-| PLoS One Human (20)       | 21.85 ± 1.70 years | Diffusion: number of connections per unit surface | Cross-correlation | 90          | Both                   | Both                           | Pearson correlation | 0.3213 ± 0.0523 | Not reported       |
| Hagmann et al. 37    | 2010 | White matter maturation reshapes structural connectivity in the late| PNAS Human (30)          | 18 months – 18 years | Diffusion: number of connections per unit surface | Cross-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.| 2013 | Abnormal rich club organization and functional brain dynamics in     | JAMA psychiatry Human (45 and 51) | 28.9 ± 7.9 years | Diffusion: number of connections per unit surface | Cross-correlation | 68 cortical and 68 + 14 subcortical | 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     | Neuro Image Human (174 and 96) | 1) 10–80 years 2) 19–85 years | Diffusion: number of connections per unit surface | Cross-correlation | 80          | Cortical + hippocampus and amygdala | Both                           | Spearman rank correlation | 1) 0.65 2) 0.49 | Not reported         |
| Zimmermann et al. 47 | 2016 | Structural architecture supports functional organization in the      | Human brain mapping Human (47) | 18–80 years (mean ± SD: 41.49 ± 18.36) | Diffusion: number of connections per unit surface | Fisher's Z transformed Pearson's correlation coefficient | 68          | Cortical               | Both                           | Spearman's correlation. | 1) Individual subjects: 0.19–0.36 (mean ± SD) 2) Group mean: 0.27 ± 0.04 (mean ± SD) for all subjects | 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    | Brain Structure and Function Human (64) | 22–36 years | Diffusion: number of connections per unit surface | Fisher's Z transformed Pearson's correlation coefficient | 113         | Cortical               | Both                           | Pearson correlation coefficient | 1) Integrated state: −0.27 (Estimated from graph) 2) Segregated state: −0.22 (Estimated from graph) | p = 6.6 × 10⁻¹⁴ |
| 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. | 2016 | Whole-brain analytic measures of network communication reveal increased structure-function correlation in right temporal lobe epilepsy. | NeuroImage: 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 |
| Goliv et al. | 2014 | Resting-brain functional connectivity predicted by analytic measures of network communication. | PNAS Human (5 and 40 and 25) | 1) 29.4 ± 3.4 years 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. | 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
| 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.           | 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          | Low resolution: 0.336 ± 0.014 (mean ± SE) | Not reported. |                  |
| Khalsa et al.        | 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 | Streamline tractography: 0.48 | 1) p = 0.005; 2) p = 0.027 |
| Hubner et al.        | 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.         | 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.
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.
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 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 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, 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 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 mice11 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 | Journal | Species (n)/Anesthesia | Structural measure (neuronal tracer) | Functional measure | Regions (n) | Cortical or subcortical | Correlation method | Correlation | p |
|--------------|------|---------|------------------------|--------------------------------------|--------------------|-------------|-----------------------|-------------------|-------------|---|
| Stafford et al.11 | 2014 | *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 | $p = 1.4136 \times 10^{-41}$ |
| Miranda-Dominguez et al.11 | 2014 | *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 (retrogradely) 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) |
| Shen et al.34 | 2012 | *The Journal of Neuroscience* | Macaque | –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 | Not reported |
| Graysen et al.55 | 2016 | *The Journal of Neuro Image* | Macaque | –1% isoflurane. | 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 | 1) TTX: 0.737 (CI: 0.55–0.854) 2) TTU: 0.613 (CI: 0.369–0.778) 3) Corico-cortical: 0.6 (CI: 0.552–0.645) 4) TTU: 0.523 (CI: 0.469–0.574) |
| Reid et al.46 | 2016 | *A cross-modal, cross-species comparison of connectivity measures in the primate brain.* | 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-Parrá et al.64 | 2017 | *Structural and functional, empirical and modelled connectivity in the cerebral cortex of the rat.* | Rat (14) / Urethane (1.2 g/kg). | Qualitative strengths 0 (non-presence) – 7 (very strong) | Fisher’s z transformed correlation coefficient | Cortical + hippocampus and amygdala | Intra-hemispheric (ROIs left and right combined) | Spearman correlation | 1) 0.48 (Present & non-presence 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) |

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).11,34,46,53,56
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. 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, 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, 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, which may influence structural network constructions. On the other hand, functional networks in the rodent and human brain are organized in a similar way. Recently, interest has been raised in comparing organizational and topological aspects of brain networks across different species, named comparative connectomics. 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 or the Allen Mouse Brain Connectivity Atlas (http://connectivity.brain-map.org). 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. 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. 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, vervet monkey, and mice. One study compared diffusion-based structural connectivity strength in humans with neuronal tracer-based structural connectivity strength in macaques. 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
inferring the direction and trajectory of white matter tracts from the diffusion of water. Recent research has demonstrated that these tractography-based structural networks do not always reflect the axonal projections between regions measured with neuronal tracers, and are especially limited in reconstructing long-distance connections. In line with this, structural networks based on diffusion-tractography are affected by many false positives, 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, 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, as well as to improve tractography methods, e.g. by using machine-learning techniques, imposing anatomical priors and constraints or applying filtering methods. Higher resolution diffusion-weighted data, such as the data acquired in the Human Connectome project, 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, 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
| First author       | Year | Title                                                                 | Journal               | Species (n)          | Age           | Structural measure (diffusion) | Structural measure (neuronal tracer) | Regions (n) | Cortical or subcortical | Correlation method | Correlation | p   |
|-------------------|------|----------------------------------------------------------------------|-----------------------|----------------------|---------------|-------------------------------|-------------------------------------|-------------|--------------------------|-----------------|-------------|-----|
| Calabrese et al.  | 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                     | Spearman-rank   | 0.42         | p < 0.05 |
| Donahue et al.    | 2016 | Using diffusion tractography to predict cortical connection strength and distance: A quantitative comparison with tracers in the monkey | The Journal of Neuroscience | 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 | Not reported |
| van den Heuvel et al. | 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 (CoCoMac) and 29 (Markov) | Cortical                 | Intrahemispheric | Correlation | 1) NOS: 0.25 (CoCoMac) | 2) p < 0.002 | 3) Streamline density: 0.31 (CoCoMac) | 4) p < 0.001 |
| Reid et al.       | 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 (0–80) | Cortical−hippocampus and amygdala | Spearman rank correlation | 0.41         | 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.

![Figure 5](image.png)

**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. 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. 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. 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. 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. 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. 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. Two of the included studies showed a slightly higher structure–function relationship for intra-hemispheric connections compared to inter-hemispheric connections, possibly because of sparse inter-hemispheric structural connectivity. In addition, two studies investigated the structure–function relationship at the single region level. They both showed a large range of structure–function relationships for connections between different regions, with correlations between 0.40 and 0.66 and between 0.2 and 0.7. 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 and the Allen brain atlas. Resting-state fMRI in small animals is more difficult. This is reflected by the relative low structure–function correlations found in mice. More sophisticated protocols and pipelines have been proposed and developed to obtain reliable and noise-free functional datasets in small animals. 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. Rodents provide unique opportunities to investigate and map structure–function relationships in specific neuronal sub-circuits, for example with optogenetics or...
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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The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Note

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

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