REVIEW

Making Sense of Connectivity

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Abstract

In addition to the assessment of local alterations of specific brain regions, the investigation of entire networks with in vivo neuroimaging techniques has gained increasing attention. In general, connectivity analysis refers to the investigation of links between brain regions, with the aim to characterize their interactions and information transfer. These may represent or relate to different physiological characteristics (structural, functional, or metabolic information) and can be calculated across different levels of granularity (2 regions vs whole brain). In this article, we provide an overview of different connectivity analysis approaches with interpretations and limitations as well as examples in pharmacological imaging and clinical applications. Structural connectivity obtained from diffusion MRI enables the reconstruction of neuronal fiber tracts. These physical links represent major constraints of functional connections, which are in turn defined as correlations between signal time courses. In addition, molecular connectivity approaches based on PET imaging enable the assessment of interregional associations of metabolic demands and neurotransmitter systems. Application of these approaches in clinical investigations has demonstrated novel alterations in various neurological and psychiatric disorders on a network level. Future work should aim for the combined assessment of multiple imaging modalities and to establish robust biomarkers for clinical use. These advancements will further improve the biological interpretation of connectivity metrics and networks of the human brain.

Keywords: connectivity, diffusion tensor imaging, graph theory, network, positron emission tomography, resting-state fMRI

Introduction

The possibility to assess human brain structure and function in vivo has made significant contributions to the clinical characterization of numerous psychiatric and neurological disorders. Imaging techniques like magnetic resonance imaging (MRI), positron emission tomography (PET), and electroencephalography are among the most used modalities. As such, they have substantially increased our knowledge about the maturation of the brain, normal physiological processes, and pathological alterations thereof. Traditionally, the focus has been on local effects and changes in certain brain regions like tumors or atrophy, alterations in blood flow and metabolism, as well as the up- or downregulation of receptors and transporters of neurotransmitter systems. Particularly with the use of functional MRI (fMRI), cognitive functions and processing of certain emotions were often ascribed to specific areas. As the brain, however, comprises far more connections than regions,

namely 10^{14} synaptic connections vs 10^{10} neurons, the investigation of these links has always been of great interest. Invasive histological approaches such as cell staining and the injection of labeled agents for tract tracing have previously been used for the assessment of anatomical networks, and these represent the very basis for the nowadays widespread connectivity analyses. One example is given by the CoCoMac database (Kötter, 2004), which combines a multitude of anatomical tract tracing studies into a comprehensive data set of physical connections within the primate brain.

It is now well established that not a single brain area but rather the concert of several anatomically and/or functionally interconnected regions is responsible for the diverse processing of external and internal stimuli as well as response and adaptation. The study of connectivity thus aims to model and understand how such a coordinated interplay and the interactions

between brain regions form neuronal networks, which in turn maintain efficient information processing. Although current in vivo brain imaging approaches cannot give a complete description of the connectome at a cellular level, these techniques are well suited to investigate brain networks at the macro-scale. The present article aims to provide an overview of common connectivity analysis strategies derived from data such as structural and functional imaging. We also highlight further aspects of connectivity obtained from PET imaging as well as multimodal combinations of these approaches. Following a brief description of each technique as well as their advantages, interpretations, and limitations, several examples with respect to applications in clinical and neuropharmacological research will be provided.

Connectivity Levels and Graph Theory

Connectivity analyses based on imaging data can be carried out on multiple levels of detail. The most specific analysis is between 2 a priori chosen brain regions yielding, for example, a single estimate of connection strength or a fiber pathway (seed-to-seed connectivity; Figure 1a). If one is, however, interested in the relation of a certain region (i.e., a seed region) compared with the rest of the brain, a connectivity map can be constructed (seed-to-voxel connectivity; Figure 1b). A more generalized approach covers the assessment of whole-brain connectivity. This can be achieved by setting up a connectivity matrix, where each matrix entry represents the connectivity between any 2 regions (Figure 1c). The approach enables the specific assessment of within- and between-network connections, for example, to investigate if pathological alterations are limited to a certain network, multiple networks independently, or may be specifically ascribed to between-network communications (Kaiser et al., 2015). Such connectivity matrices can then be further used for statistical testing, for example, with network-based statistics (Zalesky et al., 2010), or they may be subject to network analysis using graph theory. While the former approach directly operates on raw connectivity matrices, the appearance of the connectivity matrix regarding sparsity, weighting, and directionality is important for the latter. Usually, weak links are discarded since spurious connections may obscure the topology of the network (Rubinov and Sporns, 2010), though the importance of few weak ties has also been highlighted (Gallos et al., 2012). Weighted connections often provide a measure of "connectivity strength," but as this in

itself can raise difficulties regarding the interpretation (see structural connectivity), matrices are often binarized after thresholding. Regarding the directionality of connections, this can often only be achieved by invasive tract-tracing or with dynamic causal modeling. Graph theory enables the extraction of network summary metrics like node degree and network efficiency reflecting the connection strength of a single region and the interconnectedness of the entire network, respectively. These have in turn been related to intelligence scores (Li et al., 2009; Ryman et al., 2016) and cognitive performance (Hampson et al., 2006; Giessing et al., 2013), and alterations were identified in various psychiatric populations (Lord et al., 2012). A particularly interesting approach is to study network economy and the simulation of network perturbations (Bullmore and Sporns, 2012; Hahn et al., 2015a). This allows to assess cost-efficiency tradeoffs (Achard and Bullmore, 2007) and modelling of putative pathological mechanisms by inducing "lesions" in brain networks (Fornito et al., 2013; Gollo et al., 2018). Although these examples indicate that graph metrics may indeed capture physiologically relevant information, a recent study suggested caution for one of the most prominent findings, namely the association between intelligence and brain network efficiency (Kruschwitz et al., 2018). Thus, several limitations should be considered when evaluating whole-brain connectivity. These include potential pitfalls when constructing a connectivity matrix (e.g., definition of nodes and edges), during the analysis (thresholding, multiple comparisons, and null models), or when interpreting the results (when whole-brain summary measures are actually caused by local alterations) (Fornito et al., 2013). For a detailed description on graph theory and the corresponding outcome metrics (Rubinov and Sporns, 2010), please see previous seminal review articles (Sporns et al., 2004; Bullmore and Sporns, 2009; Fornito et al., 2013).

Structural Connectivity

At the structural level, diffusion weighted imaging approaches such as diffusion tensor and spectrum imaging offer the possibility to reconstruct the anatomical/physical links between brain regions. This is based on the anisotropic diffusion of water along white matter fiber tracts (for a recent review, see Shi and Toga, 2017). Reconstruction of fiber pathways is usually done with deterministic or probabilistic algorithms. The former reconstructs tracts based on the preferential diffusion direction
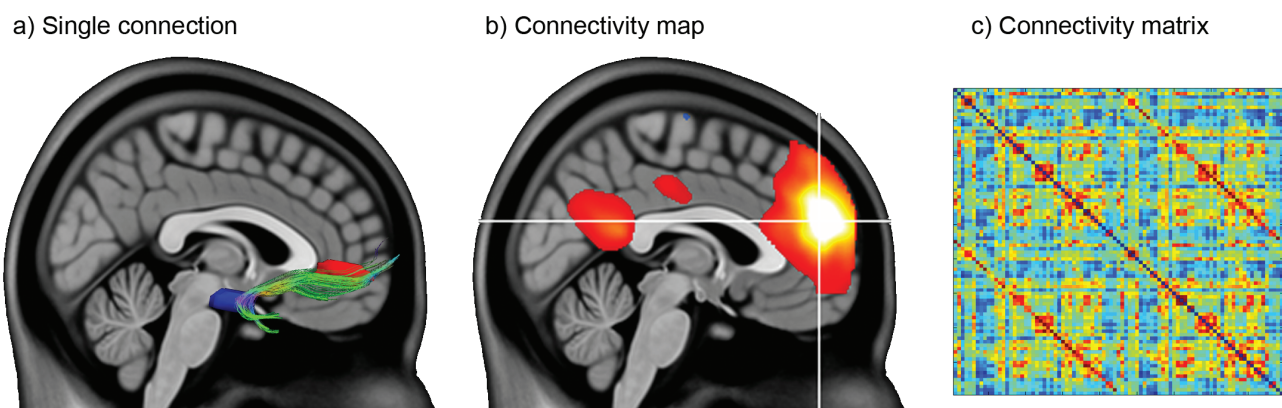
a) Single connection b) Connectivity map c) Connectivity matrix

Figure 1. Different levels of connectivity. (a) A single structural connection is shown between 2 a priori-defined brain regions: the uncinated fasciculus, connecting the amygdala (blue) with the frontal cortex (red, regions schematically drawn). (b) Functional connectivity map with respect to a particular seed region, the prefrontal cortex (illustrated by the crosshair). (c) Whole-brain connectivity matrix derived from an anatomical atlas. Each matrix entry reflects the connectivity of 2 brain regions as shown in a. Each column (and row) of the connectivity matrix represents a connectivity map as given in b.

and hence yields streamlines with equal weights forming a single tract (Figure 2a). In contrast, the latter approach models the uncertainty of local fiber directions. As a result, probabilistic tractography provides various possible fiber pathways with an estimate of the robustness of each tract against noise (Figure 2b). For both approaches, great effort has been carried out to relate connectivity metrics to actual connectivity strength. Using invasive tract tracing results as reference, a moderate association was obtained for a deterministically defined number of streamlines (van den Heuvel et al., 2015), which was however 2-fold higher for probabilistic indices (Donahue et al., 2016). On the other hand, for whole-brain connectivity matrices, the high specificity obtained with deterministic approaches seems more important than the high sensitivity inherent to probabilistic tractography (Zalesky et al., 2016). Another interesting aspect is given by the interpretation of the commonly used metric of fractional anisotropy. Using the postmortem approach CLARITY, a relationship was found with immunofluorescence-labeled myelin basic protein for commissural tracts with coherent fiber organization (Chang et al., 2017). This association with fractional anisotropy was, however, not confirmed by in vivo MRI-based estimation of myelin content (Arshad et al., 2017). Furthermore, it should be noted that the term white matter "integrity" may be used for disease-related changes in fractional anisotropy but can be misleading for interpretations related to

cognitive performance or learning (Jones et al., 2013). More generally, changes in diffusion metrics may reflect various biological aspects. These include myelination, axon diameter, packing density, and fiber organization but also changes in astrocytes and vascularization (Takahashi et al., 2002; Zatorre et al., 2012). Although these cannot be disentangled by diffusion MRI, preclinical studies have provided further insight into the underlying mechanisms, showing that learning-induced changes in white matter fractional anisotropy are related to changes in myelin staining (Blumenfeld-Katzir et al., 2011; Sampaio-Baptista et al., 2013). Moreover, the introduction of neurite orientation dispersion and density imaging may provide an even more specific surrogate of microstructure, which can still be obtained in a reasonable acquisition time (Zhang et al., 2012). Another issue that should be considered is that of crossing fibers within the brain, especially when considering that up to 90% of white matter voxels contain multiple fiber orientations (Tournier et al., 2011). Thus, dedicated algorithms that are able to reconstruct also nondominant tracts (Behrens et al., 2007) should be employed when investigating these brain regions.

Structural connectivity investigations greatly improved our understanding of brain organization and the impact of its wiring. For instance, using graph metrics, the posterior part of the default mode network was identified as structural core, emphasizing its importance in functional integration (Hagmann
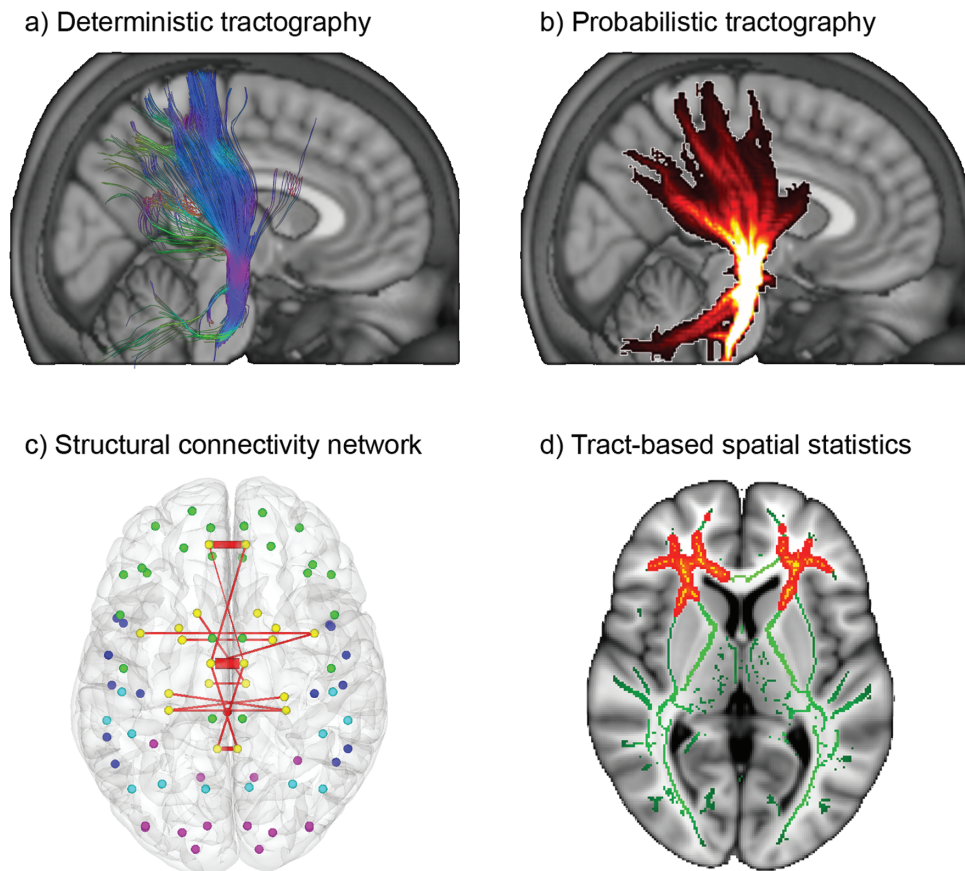
a) Deterministic tractography

b) Probabilistic tractography

c) Structural connectivity network

d) Tract-based spatial statistics

Figure 2. Structural connectivity obtained from diffusion tensor imaging. (a) Deterministic tractography with the seed region defined in the cerebral peduncle yields the corticospinal tract. Each streamline gets the same weight; color coding reflects the direction (blue, inferior-superior; green, anterior-posterior; red, left-right). (b) Probabilistic tractography of the same tract as in a, with each streamline reflecting the probability of how robustly a pathway can be reconstructed in the presence of noise (bright color: higher probability). (c) Evaluation of whole-brain structural network parameters showed increased interhemispheric connectivity in male-to-female transsexual subjects particularly subcortical-cortical connections, which where distinct from male and female controls (reprinted by permission from Oxford University Press) (Hahn et al., 2015b). (d) Tract-based spatial statistics (TBSS) enables a regional assessment of white matter microstructure. In contrast to c, the local mean diffusivity of transsexuals showed a transition from the biological sex to the actual gender identity (Kranz et al., 2014).

et al., 2008). Furthermore, sex differences in behavioral abilities seemed to be at least partly related to differences in intra- and interhemispheric wiring of the brain, with connections optimized for coordinated motor abilities and social skills in men and women, respectively (Ingalhalikar et al., 2014). This finding further extends to differences in transsexual subjects with network parameters revealing distinct characteristics (Hahn et al., 2015b) (Figure 2c), whereas regional values of fractional anisotropy mostly reflect the transition from the biological sex to the actual gender identity (Kranz et al., 2014) (Figure 2d). Further clinical examples include prediction of MDD response to selective serotonin reuptake inhibitors (SSRIs), which was achieved by modeling a specific tract between the midbrain raphe and amygdala (Delorenzo et al., 2013). Such a specific application of tractography to model certain tracts also facilitated the individual planning of electrode placement in deep-brain stimulation, leading to markedly high response rates in treatment-resistant depression (Schlaepfer et al., 2013). Other examples include automated computation of tract profiles in bipolar disorder with the advantage to investigate regionally specific differences of white matter pathways (Sprooten et al., 2016) as well as normative databases and atlases of major tracts that may serve as reference for comparison with individual patient data (Oishi et al., 2011; Figley et al., 2017).

We would like to note that the approach of tract-based spatial statistics (Smith et al., 2006) (Figure 2d) is not a connectivity analysis in the strict sense, but merely a voxel-wise evaluation of skeletonized white matter using a sophisticated spatial normalization algorithm. Still, the approach has been widely used and yielded interesting results in clinical investigations. For instance, an increased sensitivity to detect alterations in patients with major depression was demonstrated compared with the nonskeletonized voxel-based approach (Bergamino et al., 2017). Furthermore, tract-based spatial statistics results yielded differences between responders and nonresponders to ketamine (Vasavada et al., 2016) and after electroconvulsive therapy (Lyden et al., 2014) in the cingulum bundle.

Another approach to investigate structural connectivity networks is that of computing structural covariance networks, for example, with voxel-based morphometry data (He et al., 2007; Bassett et al., 2008). Here, a whole-brain connectivity matrix (Figure 1c) is compiled by calculating correlations of gray matter volumes between region pairs across an entire sample. This is based on the strong correlation of local MRI metrics for anatomically connected regions (Mechelli et al., 2005; Lerch et al., 2006). Although the technique indeed relates to biologically relevant information (Evans, 2013), structural covariance networks do not fully reflect tractography-based connections (Gong et al., 2012). The main limitations of the approach are that only a single connectivity matrix is obtained for an entire sample (but first attempts to resolve this have been introduced; Foster-Dingley et al., 2016) and the indirect information of the underlying connectivity pattern.
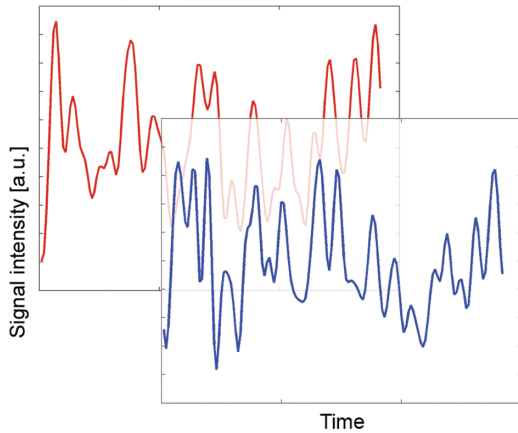
Functional Connectivity

Functional connectivity computed from resting-state fMRI is by far the most-used approach to assess brain networks. This was first described by Biswal and colleagues for the motor system (Biswal et al., 1995) and required another 10 years until it experienced a dramatic increase in its use, for example with the 1000 functional connectomes project (Biswal et al., 2010). The approach is based on the calculation of statistical metrics of signal time courses between brain regions (mostly correlation analysis, but also coherence or phase-locking) (Figure 3a). Hence, functional connectivity is highly time dependent and connectivity patterns may change even within few milliseconds, which can be captured by electroencephalography or magnetoencephalography. In contrast, structural connections are stable at shorter time scales of minutes but may be subject to changes at longer intervals, such as after prolonged training (Zatorre et al., 2012) or treatment (see above). Functional connectivity "at rest" implies the acquisition of spontaneous fluctuations in brain activity (Fox et al., 2005), which in turn means that subjects are awake but do not perform a certain task with common instructions to "let thoughts come and go freely" or "do not think of anything in particular" (Smith et al., 2013). Studying brain activity in the absence of a task, or historically the deactivation during task performance also identified with PET (Raichle et al., 2001), led to the robust identification of the default mode and various other brain networks (Yeo et al., 2011). These functional networks can also be obtained during anesthesia (Liu et al., 2017) or deep sleep, though characterized by decoupling (Horovitz et al., 2009) and specific network changes related to varying levels of arousal and consciousness (Tagliazucchi and van Someren, 2017). In addition to these networks, functional connectivity has been widely used to refine the parcellation of the human cortex (Glasser et al., 2016; Gordon et al., 2016), offering highly homogeneous areas and identification of individual neuroanatomical fingerprints.

Functional connectivity is usually computed by seed-based correlation analyses or independent component analysis, each with different aspects to keep in mind such as seed selection bias or the optimal number of independent components to be estimated (Cole et al., 2010). Regardless of the used method, data preprocessing is an essential step for functional connectivity. It is important to account for potentially confounding signals such as scanner drifts and artifacts or those with physiological origin, including motion, respiratory, and cardiovascular noise. Common approaches to minimize their influence are motion scrubbing (Power et al., 2012), nuisance regression against motion parameters, and signals obtained from separately acquired data (Glover et al., 2000) or white matter and cerebrospinal fluid signals (Weissenbacher et al., 2009), as well as bandpass filtering. For specific details, the reader is referred to seminal previous work (Murphy et al., 2013; Shirer et al., 2015; Bright et al., 2017; Caballero-Gaudes and Reynolds, 2017). Of note, motion may represent an issue that requires thorough attention, especially when investigating children, the elderly, or certain clinical populations (Power et al., 2012). Another issue that may require further investigation in the future is to include white matter signal in the nuisance regression due to similar activation in gray and white matter (Courtemanche et al., 2018; Ding et al., 2018). Global signal regression, on the other hand, has been demonstrated to introduce potentially spurious anti-correlations (Weissenbacher et al., 2009; Cole et al., 2010) and renders the interpretation of group comparisons difficult (Saad et al., 2012) and is therefore rarely used anymore.

Functional connectivity also enables a dynamic assessment over short time scales and in response to pharmacological treatment. It has been demonstrated that functional connectivity is not a static phenomenon, but connections may rapidly switch between repeatedly occurring states (Hutchison et al., 2013; Calhoun et al., 2014) and these are hierarchically organized in time (Vidaurre et al., 2017). The evaluation of such dynamic states has also revealed novel aspects of mental disorders. For instance, combining topological properties of static and dynamic connectivity differentiated major depression patients with and
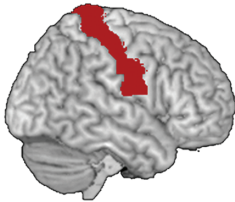
a) Resting-state fMRI signals

d) Ketamine-dependent phfMRI response
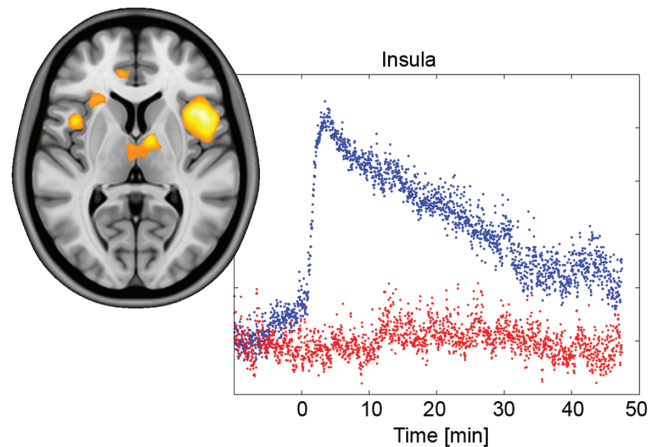
b) Somatosensory seed

c) Ketamine-induced functional connectivity across time
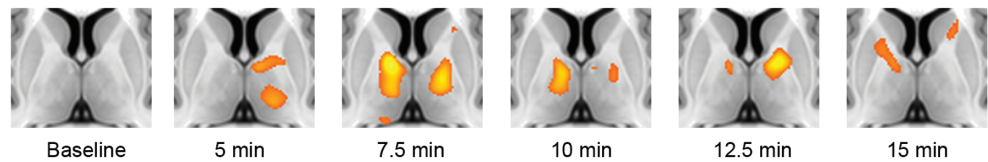

Figure 3. Functional connectivity obtained from functional MRI. (a) Resting-state signal time course of 2 different brain regions from the default mode network (red, posterior cingulate cortex; blue, medial prefrontal cortex). The temporal correlation of these signals is used as index of functional connectivity. (b) Anatomical seed regions of large cortical regions (here the somatosensory cortex) can be used to map small thalamic nuclei. (c) Using the seed region in b, changes in functional connectivity following an acute i.v. challenge of ketamine compared with placebo reflect those seen in schizophrenia patients (reprinted by permission from Springer) (Hoflich et al., 2015). (d) Pharmacological functional MRI (fMRI) shows that neuronal activation followed that of ketamine plasma levels in the insula, anterior cingulate, and thalamus. Scatterplot shows an exemplary time course of the insula with ketamine and placebo response in blue and red, respectively (reprinted by permission from Oxford University Press) (Hoflich et al., 2017).

without suicidal ideation (Liao et al., 2018), and dynamic connectivity may even have the potential to outperform the static connectivity analysis as, for example, in posttraumatic stress disorder (Jin et al., 2017).

As a limitation, and similar to structural connectivity assessed with diffusion imaging, functional connectivity is nondirectional, that is, more sophisticated models are required for inference on the direction of information flow. This can, however, be used as an advantage for certain investigations. It is particularly difficult to define small subcortical structures and nuclei of the brainstem and the thalamus, although their anatomical projections are well known. Using the above characteristic of nondirectionality, one can use large cortical projection areas as seed regions to functionally (or anatomically) (Behrens et al., 2003) identify thalamic nuclei. The approach has been proven useful in an investigation of schizophrenia patients. Where previous studies only suggested general thalamic dysfunction in these patients, the approach showed that alterations specifically include thalamic connections to the prefrontal, motor, and somatosensory cortices (Woodward et al., 2012). Using i.v. application of ketamine in healthy subjects as a model for schizophrenia, similar changes were observed for the thalamic projections to the somatosensory cortex (Figure 3b–c) (Hoflich et al., 2015), emphasizing the involvement of the NMDA receptor and potential secondary glutamatergic effects in schizophrenia.

Resting-state fMRI has also been used to model acute drug effects during the measurement (pharmaco fMRI). Although most of the work to date has not employed connectivity analyses

per se, this may represent an interesting future opportunity to study drug effects on a network level (Schwarz et al., 2007; Hoflich et al., 2015). Current applications have already demonstrated great insight into the association between brain response and neurotransmitter system actions specific to pharmacological effects. These include studies of amphetamine and SSRIs in rodents (Schwarz et al., 2007) as well as human investigations of SSRIs (McKie et al., 2005) and ketamine (Deakin et al., 2008). The latter has also received particular interest due to its rapid antidepressant effects (Zarate et al., 2006) with models derived from previous data (De Simoni et al., 2013) or directly from ketamine plasma levels (Höflich et al., 2017). Regardless of the model, all of these investigations identified important nodes of ketamine action such as the thalamus and insula as well as a negative response in the subgenual anterior cingulate cortex (Figure 3d). This is in line with a large body of literature showing the importance of the subgenual anterior cingulate and its connectivity in the pathophysiology (Murrough et al., 2016) and treatment of major depression (Dunlop et al., 2017). In this context, functional connectivity has been successfully used to model antidepressant effects of ketamine (Scheidegger et al., 2012) and to predict treatment response to psilocybin (Carhart-Harris et al., 2017). Interestingly, these 2 treatment agents elicited decreased and increased functional connectivity, respectively, which may be related to their different modes of action via NMDA and serotonin-2A receptors. Another therapy option for treatment-resistant patients is given by electroconvulsive therapy, which showed changes predominantly in various regions of the default

mode and executive control networks (Perrin et al., 2012; Mulders et al., 2016; Wang et al., 2018). Particularly interesting findings have also been obtained for invasive (deep-brain stimulation) and noninvasive brain stimulation (transcranial magnetic and transcranial direct current stimulation), showing that different effective sites for both stimulation types were part of the same functional networks (Fox et al., 2014). Moreover, functional connectivity between different transcranial magnetic stimulation sites and the subgenual anterior cingulate cortex predicted its effectiveness in depression (Fox et al., 2012). These findings demonstrate the usefulness of connectivity analyses in clinical populations, further improving patient care and treatment success. This is supported by recent advances to use functional connectivity for individual prediction of behavioral or clinical scores (Shen et al., 2017), identification of patient subtypes in major depression, as well as response to transcranial magnetic stimulation (Drysdale et al., 2017).

Similar to the above stimulation techniques, functional connectivity changes can also be provoked by mood induction paradigms, where data acquisition is carried out right after specific stimulation (Figueroa et al., 2017; Krause et al., 2018). These applications are likely to yield important clinical information since they are between resting-state and task-specific connectivity. Furthermore, task-relevant connectivity can be obtained during continuous stimulation or task performance rather than afterwards (Shirer et al., 2012; Hahn et al., 2018), which may capture stimulation effects even more precisely. Although connectivity estimates from conventional task fMRI block designs also gained attention (Fair et al., 2007; Braun et al., 2015), these may include potential difficulties in the interpretation due to the alternation of rest and task. Such designs exhibit high-frequency components not seen in continuous resting-state and hence also significant differences (Ganger et al., 2015), which needs to be kept in mind when investigating patient populations (Loitfelder et al., 2014).
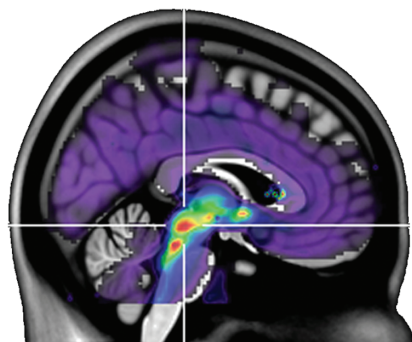
Molecular Connectivity

Analogous to structural covariance networks (see Structural Connectivity above), it is possible to compute interregional
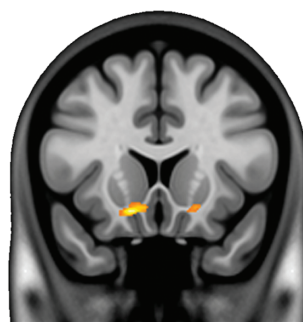
associations based on molecular information from PET imaging. The approach reaches back to early work in the 1980s and is based on the observation that brain regions with similar metabolic demands are also functionally coupled (Macko et al., 1982; Horwitz et al., 1984). Using the radioligand [^{18}F]FDG has led to important insights into the brain's organization on a metabolic level (Lee et al., 2008). Interestingly, direct comparison between networks identified on the basis of glucose metabolism and functional connectivity revealed mixed findings, either with high overlap (Savio et al., 2017) or divergence (Di and Biswal, 2012) especially for the default mode network. The approach has further been used, for example, in Alzheimer's disease showing reduced metabolic connectivity (Morbelli et al., 2012) but also the potential of cognitive reserve in bilingual patients with increased connectivity despite more pronounced hypometabolism (Perani et al., 2017). Furthermore, metabolic networks exhibited a compensatory mechanism in the nonaffected hemisphere in unilateral temporal lobe epilepsy (Vanicek et al., 2016), which parallels findings of functional connectivity (Bettus et al., 2009).

The technique has also been extended to a neurotransmitter level using known anatomical connections. For instance, serotonergic neurons have their cell bodies in the raphe nuclei, projecting to almost the entire brain. There, 2 key players of serotonergic neurotransmission and cell firing are the serotonin-1A receptor and transporter (Figure 4a), exhibiting an autoinhibitory function (Evans et al., 2008) and regulating extracellular serotonin (Tao et al., 2000), respectively. Such changes in cell firing, and presumably serotonin release, may in turn affect the expression of binding sites in cortical and subcortical regions. Hence, the well-known neurotransmitter pathways can be used as a priori hypothesis to map the association of serotonergic binding proteins between the raphe nuclei and projections areas. This approach has shown a strengthened association of the serotonin-1A receptor between the dorsal raphe nucleus and the amygdala and hippocampus after SSRI administration (Hahn et al., 2010), complementing regional changes in patients with anxiety disorder after treatment (Spindelegger et al., 2009) on a network level. Similarly, in patients with major depression, an altered association of the serotonin transporter was found
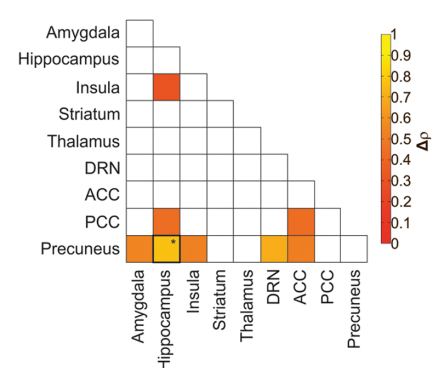

Figure 4. Molecular connectivity obtained from PET imaging. (a–b) Interregional associations were assessed on the basis of known serotonergic projections. (a) Serotonin transporter (SERT) binding of the dorsal raphe nucleus (indicated by crosshair) was used as seed region. (b) Decreased SERT associations between the dorsal raphe and the ventral striatum were observed in patients with major depression (reprinted by permission from Wiley) (Hahn et al., 2014). (c) The approach was further extended to various SERT-rich brain regions, showing a decreased association between the precuneus and hippocampus in patients with attention deficit/hyperactivity disorder (reprinted by permission from Wiley) (Vanicek et al., 2017).

specifically in the ventral striatum (Hahn et al., 2014) (Figure 4b), suggesting a serotonergic involvement (Kranz et al., 2010) of diminished reward processing in these patients.

Similar to connectivity mappings of glucose metabolism, interregional associations of neurotransmitter systems have also been calculated across several regions and entire brain maps (Bose et al., 2011). For instance, longitudinal characterization of serotonin transporter occupancy induced by SSRIs showed increased correlations in networks of the anterior cingulate cortex and the insula in patients with major depression (James et al., 2017). The usefulness of such an investigation was also evident in attention deficit/hyperactivity disorder with altered interregional associations between the precuneus and hippocampus despite no difference in regional serotonin transporter binding (Vanicek et al., 2017) (Figure 4c). This links changes of the default mode network in these patients (Castellanos et al., 2008; Sudre et al., 2017) to a specific serotonergic contribution. Further expanding the approach to a whole-brain investigation, it has been suggested that interregional correlations of amyloid-β binding may be used to assess disease progression in Alzheimer's disease (Son et al., 2015; Pereira et al., 2018) and novel relationships between the serotonin and opioid neurotransmitter systems were revealed in healthy subjects (Tuominen et al., 2014).

As mentioned in the section of structural covariance networks, the main limitation of the method is that inference can only be drawn at the group level as covariance matrices cannot be obtained for individual subjects. Hence, the observed associations may reflect molecular connections only indirectly. In this context, the term "connectivity" may be used with care when compared with that of other modalities and should not be used synonymously with, for example, structural connectivity. While molecular connectivity of glucose metabolism has been well characterized, the biological interpretation for interregional associations, especially whole-brain applications, of other radioligands may require further investigations. Another limitation of the approach is that correlated noise between regions may introduce falsely increased correlations. Furthermore, the potential issue of differences in input functions or nonspecific binding should be considered, especially when performing group comparisons, for example, with random permutations. Randomly mixing 2 groups with different average regional values may introduce inflated correlations for random permutations, which will finally yield false negative results.

Mulitmodal Combinations

A particular appealing approach is given by the combination of various imaging modalities to study connectivity from different complementary perspectives. Among these, structure-function relationships have been investigated most intensively. Functional connections can theoretically be obtained independent of (i.e., without) direct anatomical/structural connections, since the former are usually calculated as correlations. However, missing structural connections markedly affect functional ones, probably best described in surgical sections of the corpus callosum (Johnston et al., 2008; Roland et al., 2017), demonstrating that physical links represent important constraints of functional connectivity. As such, major resting-state networks are connected by well-known anatomical links (van den Heuvel et al., 2009). On the other hand, functional connectivity can also result from indirect anatomical connections (Greicius et al., 2009), which underlines that structural and functional connections do not resemble in a simple one-to-one mapping (Ajilore

et al., 2013). Furthermore, functional connectivity is subject to a larger variability across subjects than structural connectivity (Chamberland et al., 2017). More importantly, functional connectivity is most similar to the underlying anatomy during anesthesia, whereas wakefulness is characterized by rich functional configurations that deviate from structural connections (Barttfeld et al., 2015). These issues may explain why previous assessments of structure-function relationships with simply correlation analysis showed varying degrees of associations (Hagmann et al., 2008; Brown et al., 2012) and more sophisticated models are required to predict brain function from the underlying anatomy. Examples include nonlinear neuronal mass models (Honey et al., 2009), structurally-derived measures of network communication (Goñi et al., 2014), and anatomically weighted functional connectivity (Bowman et al., 2012). Structure-function relationships have also been investigated for specific brain regions and networks such as the medial temporal lobe (Shah et al., 2018), angular gyrus and intraparietal sulcus (Uddin et al., 2010), supplementary motor area (Johansen-Berg et al., 2004), posterior cingulate cortex (Khalsa et al., 2014), and the thalamus (D. Zhang et al., 2010), demonstrating the usefulness of combined analyses, for example, to refine parcellation of brain regions as well as their interactions.

In addition to the combined assessment of brain structure and function, it is of further importance to evaluate which other physiological characteristics such as neurotransmitter distribution may affect or constrain connectivity. For instance, it has been demonstrated that brain regions with overall higher excitatory than inhibitory receptor expression showed higher functional connectivity (van den Heuvel et al., 2016). Specific associations have also been reported for the serotonin-1A receptor subtype with distinct influence on the posterior default mode network, depending on its effect with respect to autoinhibition on serotonergic cell firing or local inhibition (Hahn et al., 2012). Similar associations have been reported for the anterior part of this network with dopamine D_1/D_2 receptors (Nagano-Saito et al., 2009), the cathechol-O-methyltransferase genotype (Liu et al., 2010), and gamma aminobutyric acid during emotional processing (Northoff et al., 2007). This multitude of interactions draws a complex picture of how functional connectivity is regulated in healthy subjects. Beyond that, altered associations between neurotransmitter binding proteins and functional connectivity have been reported in several mental disorders. Recent examples include an opposite correlation of the serotonin transporter in mild cognitive impairment (Barrett et al., 2017) and of serotonin-2A receptor gene variants in posttraumatic stress disorder (Miller et al., 2016) compared with controls.

Another interesting approach is to investigate the relationship between functional connectivity and metabolic demands (Tomasi et al., 2013; Aiello et al., 2015; Nugent et al., 2015; Passow et al., 2015; Soddu et al., 2016). It is however worth mentioning that most work evaluated this association with a focus on spatial dependency (i.e., across brain regions), hence, reporting correlations with high significance, but this was sometimes reached by using a vast amount of voxels in the brain. In contrast, investigations across subjects showed a different picture with lower associations (Tomasi et al., 2013; Aiello et al., 2015). The latter is also in line with a partial mismatch regarding the activated regions and connectivity during stimulation in rodents (Wehrl et al., 2013). Despite a similar lack of correlation between glucose metabolism and functional connectivity in humans, regional metabolic changes during task performance were accompanied by changes in functional connectivity and white matter microstructure of the corresponding connections,

identifying specific brain networks involved in stimulus processing (Hahn et al., 2018). Combining local metabolic information with functional connectivity may further enable to draw inferences on hierarchical information processing (bottom-up vs top-down) between brain regions (Riedl et al., 2016).

Finally, genetic variants have been shown to be associated with brain connectivity. For instance, global graph metrics are considerably heritable (Sinclair et al., 2015), and functional connectivity differences between adolescents and adults are dependent on genetic variations (Meyer et al., 2016). Moreover, functional connectivity is reflected by transcriptional variation of gene expression specifically for genes enriched in the upper cortical layers (Krienen et al., 2016) and for those involved in ion channel and synaptic activity (Richiardi et al., 2015). The influence of genetic variations on brain connectivity has also been shown in clinical populations, where the genetic risk profile for schizophrenia correlates with functional connectivity (Rashid et al., 2019) and serotonin 2A receptor gene variants moderate default mode connectivity in posttraumatic stress disorder (Miller et al., 2016). As in most studies using imaging genetics, a high sample size is required to demonstrate the often small effects sizes of genetic variants. Thus, the approach may particularly benefit from the recently growing data sharing initiatives.

Conclusions and Future Directions

To summarize, connectivity approaches provide important information on the organization of the human brain on a network level. Investigating the connections and interactions between brain regions offers additional knowledge that cannot be obtained from regional analyses alone. The different connectivity methods contain complementary information about brain structure and function as well as metabolic and molecular insights. That is, structural methods offer delineation of physical neuronal pathways, which has been successfully used as guide for individual neurosurgery plans for deep brain stimulation (Schlaepfer et al., 2013). On the other hand, functional connectivity reflects the correlation between signal time courses across brain regions. Resting-state connectivity represents a particularly promising approach for clinical use due to the rather simple data acquisition. That is, no complex paradigms or stimulation are required and there is no bias induced by task performance; however, potential pitfalls in data processing should be taken into consideration (Shirer et al., 2015; Bright et al., 2017). As the assessment of dynamic functional connectivity is a growing field, an important aspect of future work will be to harmonize procedures to capture such temporal variations. For instance, these include the computation of connectivity (instantaneous phase synchrony, independent component analysis, sliding window with challenges regarding the window type, length, and overlap), choice of appropriate null models for validation, and interpretation of different brain states (Keilholz et al., 2017; Preti et al., 2017). Such advancements will improve the reproducibility of dynamic connectivity and thus the discrimination of patient populations. Finally, molecular approaches based on PET imaging provide information on interregional associations of metabolic demands and neurotransmitter systems. The later technique may be particularly useful to further investigate the complex regulation of functional connectivity by different neurotransmitters. These techniques may be particularly useful to determine the underlying neurotransmitter actions of the otherwise unspecific functional connectivity obtained from BOLD imaging. Further advances in this direction are important

to improve the biological interpretation of the different connectivity approaches.

With respect to clinical applications, alterations of brain connectivity have been successfully demonstrated in various patient populations and in response to pharmacological treatments. A major objective of future work should be to establish robust biomarkers to aid clinical diagnose and choice of therapy. Most studies focus on a single imaging modality; however, the multimodal assessment such as the dissociations between structural and functional connectivity may reveal novel pathological aspects of psychiatric and neurological disorders (Vega-Pons et al., 2016). Furthermore, a recent study reporting connectivity-based subtypes of major depression (Drysdale et al., 2017) could not be replicated (Dinga et al., 2018). Such attempts for replication and methodological developments for individual prediction (Shen et al., 2017) represent important advancements to enable the future use of connectivity metrics in clinical settings.

Statement of Interest

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