



SPECIAL ISSUE ARTICLE

A theoretical rut: revisiting and critically evaluating the generalized under/over-connectivity hypothesis of autism

Giorgia Picci, Stephen J. Gotts and K. Suzanne Scherf

Department of Psychology, Pennsylvania State University, USA

Abstract

In 2004, two papers proposed that pervasive functional under-connectivity (Just et al., 2004) or a trade-off between excessive local connectivity at the cost of distal under-connectivity (Belmonte et al., 2004) characterizes atypical brain organization in autism. Here, we take stock of the most recent and rigorous functional and structural connectivity findings with a careful eye toward evaluating the extent to which they support these original hypotheses. Indeed, the empirical data do not support them. From rsfMRI studies in adolescents and adults, there is an emerging consensus regarding long-range functional connections indicating cortico-cortical under-connectivity, specifically involving the temporal lobes, combined with subcortical-cortical over-connectivity. In contrast, there is little to no consensus regarding local functional connectivity or findings from task-based functional connectivity studies. The structural connectivity data suggest that white matter tracts are pervasively weak, particularly in the temporal lobe. Together, these findings are revealing how deeply complex the story is regarding atypical neural network organization in autism. In other words, distance and strength of connectivity as individual factors or as interacting factors do not consistently explain the patterns of atypical neural connectivity in autism. Therefore, we make several methodological recommendations and highlight developmental considerations that will help researchers in the field cultivate new hypotheses about the nature and mechanisms of potentially aberrant functional and structural connectivity in autism.

Research highlights

- Just *et al.* (2004) and Belmonte *et al.* (2004) proposed specific hypotheses of atypical connectivity patterns in autism.
- We review the most recent and rigorous resting-state, task-based, and structural connectivity findings in autism.
- The empirical data do not support these original hypotheses.
- We recommend alternative ways to study and interpret neural connectivity in autism, emphasizing the importance of evaluating individual differences and developmental mechanisms.

Introduction

In 2004, two papers presented hypotheses suggesting that a core feature of autism lies in atypical neural

connections, which could generate the phenotypic profile of the disorder (Belmonte, Allen, Beckel-Mitchener, Boulanger, Carper *et al.*, 2004; Just, Cherkassky, Keller & Minshew, 2004). The first of these two papers was an empirical fMRI study that evaluated the neural basis of language processing in adults with autism (Just *et al.*, 2004). In it the authors reported lower functional connectivity (i.e. temporal synchronization in functional activation) between frontal and parietal neural regions (a subset of 10 of 186 pairs of regions tested) in the participants with autism compared to the typical group. Based on these findings, the investigators proposed that ‘any facet of psychological or neurological function that is dependent on the coordination or integration of brain regions is susceptible to disruption, particularly when the computational demand of the coordination is large’ (Just *et al.*, 2004 p., 1817). The authors speculated that this observed *functional under-connectivity* was likely related to white matter abnormalities.

Address for correspondence: K. Suzanne Scherf, Department of Psychology, The Pennsylvania State University, 111 Moore Bldg., University Park, PA 16802, USA; e-mail: suzyscherf@psu.edu

The second paper was a conceptual paper that argued for making distinctions between long-range and local connections and between physical and computational connectivity (i.e. functional connectivity) (Belmonte *et al.*, 2004). They described long-range connections as occurring ‘between functional brain regions’ and local connections as occurring ‘within neural assemblies’. Physical connections include synapses and fiber tracts, while computational connections involve ‘information transfer’. The authors proposed that the functional under-connectivity observed by Just and colleagues was long-range and hypothesized that it could be caused by hyperactive local connections. Specifically, they argued that excessive physical connectivity at the local level could lead to undifferentiated neural regions, prohibiting the development of effective long-range connections between distal neural subregions (Belmonte *et al.*, 2004). For example, they argued that regions in sensory cortex are a likely locus of excessive local connectivity. As a result, they never become physically connected to regions in association cortex, thereby limiting effective functional communication between these regions.

Since their publication, together these two papers have been cited more than 1900 times and atypical neural connectivity has become regarded as a general principle of brain organization in autism and other disorders such as schizophrenia, bipolar disorder, and depression (e.g. Anticevic, Cole, Repovs, Savic, Driesen *et al.*, 2013; Di Martino, Yan, Li, Denio, Castellanos *et al.*, 2014; Satterthwaite & Baker, 2015; Vargas, Lopez-Jaramillo & Vieta, 2013). Similarly, functional connectivity studies have come to dominate the systems neuroscience of typical development and adult functioning (e.g. Fair, Bathula, Mills, Dias, Blythe *et al.*, 2010; Power, Schlaggar & Petersen, 2014; Sporns, Chiavlo, Kaiser & Hilgetag, 2004; Stevens, Pearlson & Calhoun, 2009). The shift to thinking about functional interactions between brain regions rather than simpler, feed-forward modular functioning has undoubtedly had positive benefits, forcing researchers to think about the dynamics of neural systems. However, the idea that the brain is highly interactive is hardly novel, and even early neuropsychologists and neurologists appreciated that local deficits could be propagated to downstream brain regions, thereby having distal effects (e.g. concepts of ‘diaschisis’: von Monakow, 1914, and ‘sejunction’: Wernicke, 1900). Given the modern prevalence of clinical studies showing altered patterns of functional connectivity across a wide range of disorders in addition to autism, it is now clear that proposals of altered connectivity require greater specificity in order to provide mechanistic insight. For example, if atypical neural connectivity is truly a causal mechanism of a disorder, researchers need to be able to

address why a particular pattern of altered connectivity leads to one specific disorder and not another.

Along these lines, we argue that it is time to take stock of the research inspired by the Just and Belmonte papers and evaluate the extent to which the now extensive literature supports their specific claims. There have already been several reviews of the empirical evidence of atypical connectivity in autism (Maximo, Cadena & Kana, 2014; Mohammad-Rezazadeh, Frohlich, Loo & Jeste, 2016; Müller, Shih, Keehn, Deyoe, Leyden *et al.*, 2011; Rane, Cochran, Hodge, Haselgrove, Kennedy *et al.*, 2015; Vasa, Mostofsky & Ewan, 2016; Vissers, Cohen & Geurts, 2012). Critically, most of these were published before the release of the Autism Brain Imaging Data Exchange (ABIDE), which includes resting-state functional imaging data from 539 individuals with autism and 573 typically developing control individuals for the purpose of data sharing with the broader scientific community. The release of these data has spurred a flurry of neural connectivity findings in autism that are relevant for these hypotheses (see Di Martino *et al.*, 2014). In addition, since the publication of prior reviews, several significant methodological advances and data processing standards have emerged that have significantly impacted the way functional connectivity findings are understood and interpreted. Specifically, there is a new understanding about how motion artifacts influence the analysis of functional connectivity data, particularly in terms of the computation of long-range connectivity, especially in developmental and resting state studies (Power, Barnes, Snyder, Schlaggar & Petersen, 2012, 2013; Satterthwaite, Wolf, Loughhead, Ruparel, Elliott *et al.*, 2012; Van Dijk, Sabuncu & Buckner, 2012). As a result, careful attention to the treatment of motion and other artifacts in the scanner and in the pre-processing of data has become *required* of researchers using functional and structural connectivity techniques (see Power, Schlaggar & Petersen, 2015 for a recent review). Therefore, with the release of massive datasets and powerful statistical and methodological approaches for dealing with motion and noise in fMRI data, there are marked differences in the standards for connectivity studies as recently as 2–3 years ago. The bulk of this new evidence has not been reviewed to date, which is important because it may provide the most rigorous and relevant findings that can reflect on these early hypotheses. Finally, given that autism is a developmental disorder and that the Belmonte *et al.* (2004) paper made developmental predictions, unlike previous reviews, we will evaluate these data in the context of the emerging developmental longitudinal neuroimaging data, particularly from diffusion imaging studies but also functional connectivity studies, from TD individuals

to understand whether these predictions are well founded given what we know about how typical brain development occurs.

Here we review these new functional and structural connectivity studies with a careful eye toward evaluating the extent to which they support the original atypical connectivity hypotheses. We have two primary goals. First, we review fMRI/MEG findings in order to evaluate the consistency (or lack thereof) with which they support the original hypotheses of either pervasive under-connectivity (Just *et al.*, 2004) and/or local over-connectivity combined with long-range under-connectivity (Belmonte *et al.*, 2004) in the neural circuitry of individuals with autism. Second, given the distinction between structural and functional connectivity provided by Belmonte and colleagues (termed ‘physical’ and ‘computational’ connectivity by them, respectively) and the suggestion by Just and colleagues that weak functional connectivity is likely related to white matter abnormalities, we also review evidence comparing the micro- and macro-structural properties of white matter fiber tracts acquired via diffusion imaging. Specifically, we evaluate whether there are higher micro-structural properties (e.g. fractional anisotropy, mean diffusivity) within local regions, indicating potential local over-connectivity, and/or lower structural properties in fiber tracts that traverse long distances (e.g. the inferior longitudinal fasciculus), indicating potential long-range under-connectivity. Finally, we discuss these findings in the context of understanding autism as a *developmental* disorder and the extent to which the findings fit in the context of what we know about the developing brain. We conclude by providing recommendations for methodological standards and conceptual approaches that can guide researchers going forward in this important line of work investigating potential atypicalities in the organization of the autistic brain.

Reviewing the evidence

Article selection

In this review, our discussion of the connectivity literature is limited to the studies published from 2011 and beyond because these are the studies that address the aforementioned methodological concerns. Searches for studies to be included were conducted on PubMed including terms such as autism, connectivity, MRI, fMRI, MEG. Studies included in the present review had to conform to the following selection criteria: (1) published in an English peer-reviewed journal; (2) included participants with a formal autism diagnosis

based on the diagnostic criteria of the DSM-III-R, DSM-IV, or DSM-V using standardized diagnostic instruments; (3) used MRI or MEG to examine patterns of connectivity; (4) reported results from MRI or MEG connectivity analyses; (5) included a minimum of ~15 subjects with autism; (6) included a group of matched typically developing (TD) participants to compare to the subjects with autism.

Of note, in conducting a review of this literature, we chose not to include studies using EEG, although there are studies that report coherence measures reflecting on issues of connectivity in autism (e.g. Coben, Clarke, Hudspeth & Barry, 2008; Mathewson, Jetha, Drmic, Bryson, Goldberg *et al.*, 2012; Murias, Webb, Greenson & Dawson, 2007). For MEG, which has better spatial resolution of source estimates than EEG, cross-talk of adjacent sources contributing to functional connectivity can contaminate and mimic functional connectivity estimates within a 5–6 centimeter distance (Ghuman, McDaniel & Martin, 2011). For EEG, this cross-talk is expected to be substantially broader, making it difficult to distinguish between changes in signal power at a single source and a change in functional connectivity between distal sources, thereby undermining the assessment of the local versus distal connectivity. Given that the hypotheses under investigation are about spatial distance in the brain, MRI and MEG are the best tools for evaluating and settling this debate, and we consider distance between sources as a factor more explicitly in reviewing the results of MEG studies.

The paper is organized as follows. First we discuss the significance of studying neural connectivity in autism and provide definitions of important terms and concepts relevant to the study of neural connectivity. Next, we review the most recent and methodologically rigorous findings regarding the functional under-connectivity and local over-connectivity hypotheses. We organize these findings in terms of the methodology used beginning with resting-state connectivity studies followed by task-based connectivity studies. Finally, we review the evidence from structural connectivity studies and evaluate the extent to which it supports (or negates) the claims of white matter involvement in functional connectivity atypicalities in autism. In Table 1, we outline all of the studies reviewed including: the imaging method(s), sample size, age range, ROIs, connectivity approach, and whether the studies converge with the under/over-connectivity hypotheses.

Neural connectivity: significance and definitions

To date, much of the neuroimaging work investigating atypical neural functioning in autism has focused on

Table 1 Outline of the studies reviewed: organized by primary method

Citation	Method	N	Age range	ROIs	Approach	Under-Connectivity	Over-Connectivity
Abrams <i>et al.</i> , 2013	rsfMRI	20 ASD 19 TD	Mean 9.9	Right & left pSTS	Whole brain seed-based approach with pSTS seeds	X (long-range)	
Alaerts <i>et al.</i> , 2013	rsfMRI	293 ASD 321 TD*	Mean 21.7	Right pSTS	Whole brain seed-based approach with right pSTS seed	X (long-range)	
Anderson <i>et al.</i> , 2011	rsfMRI	40 ASD 40 TD	12–42	Whole brain	Pairwise connectivity among 7266 regions.	X (long-range)	
Bos <i>et al.</i> , 2014	rsfMRI	27 ASD 29 TD	6–16	10 networks from ICA	Within and between network connectivity using permutation testing	X (long-range)	
Cheng <i>et al.</i> , 2015	rsfMRI	418 ASD 509 TD	7–64	Whole brain	All voxel combinations	X (long-range)	X (long-range)
Chien <i>et al.</i> , 2015	rsfMRI	40 ASD 42 TD	9–17	Right TPJ	Whole brain seed-based approach with TPJ seed		X (long-range)
Delmonte <i>et al.</i> , 2013	rsfMRI	28 ASD 27 TD	Mean 17.3	30 seed regions (e.g., ACC, MFG, Pcg, OFC)	Connectivity between seeds and striatum (NAcc and caudate)		X (long-range)
Di Martino <i>et al.</i> , 2014	rsfMRI	539 ASD 573 TD	7–64	Right medial and superior PFC, posterior cingulate, left insula & thalamus	Whole-brain voxelwise maps quantified within- and between-group striatal connectivity differences for three caudate and three putamen seeds for each hemisphere	X (local)	X (local)
Di Martino <i>et al.</i> , 2011	rsfMRI	20 ASD 20 TD	7–12	Basal ganglia	Whole brain seed-based analyses using several basal ganglia seeds		X (long-range)
Ebisch <i>et al.</i> , 2011	rsfMRI	14 ASD 15 TD	12–20	Anterior and posterior insula	Whole brain seed-based analyses	X (long-range)	
Gotts <i>et al.</i> , 2012	rsfMRI	31 ASD 29 TD	12–23	Social brain regions	Whole brain average correlation measures	X (long-range)	
Hahamy <i>et al.</i> , 2014	rsfMRI	68 ASD 73 TD	Mean 26.3	Inter- and intra-hemispheric regions	Homotopic interhemispheric connectivity	X (long-range)	
Keown <i>et al.</i> , 2013	rsfMRI	29 ASD 29 TD	Mean 13.5	Whole brain	All voxel combinations	X (local)	X (local)
Long, <i>et al.</i> , 2016	rsfMRI	64 ASD 64 TD	7–31	Whole brain	Voxel combinations defined by anatomical mask with short-range, medium-range, and long-range connections	X (long-range & local)	
Lynch <i>et al.</i> , 2013	rsfMRI	20 ASD 19 TD	7–12	PCC, Retinosplenic cortex, and precuneus seeds	Whole brain seed-based approach with each seed	X (local, long-range)	X (long-range)
Maximo <i>et al.</i> , 2013	rsfMRI	29 ASD 29 TD	Mean 13.8	Whole brain	Regional Homogeneity (ReHo) and local density analyses to evaluate to local connectivity across 12 analysis pipelines	X (long-range)	X (local)
Nair <i>et al.</i> , 2013	rsfMRI	22 ASD 23 TD	9–17	5 cortical seeds and thalamic mask	Connectivity between seed regions and thalamus	X (long-range)	X (long-range)
Nomi & Uddin, 2015	rsfMRI	72 ASD 72 TD	7–39	18 networks per age group from ICA	Between and within network connectivity	X (long-range)	X (long-range)
Padmanabhan <i>et al.</i> , 2013	rsfMRI	42 ASD 48 TD	8–36	Striatum	Whole brain, seed-based approach using 12 ROI seed regions with striatum	X (long-range)	X (long-range)

Table 1 (Continued)

Citation	Method	N	Age range	ROIs	Approach	Under-Connectivity	Over-Connectivity
Rudie <i>et al.</i> , 2013	rsfMRI	42 ASD 37 TD	9–18	264 functional regions	Whole-brain parcellation scheme	X (long-range)	X (long-range)
Tyszka <i>et al.</i> , 2014	rsfMRI	19 ASD 20 TD	Mean 27.4	Whole brain	Dual regression approach and atlas based inter-regional correlation analyses	X (long-range)	
You <i>et al.</i> , 2013	rsfMRI	15 ASD 16 TD	9–13	Whole brain and 9 seeds (e.g., OFG, premotor, SMA, posterior MTG)	Seed-based connectivity (distant) and voxel-wise whole brain (local)		X (long-range and local)
von dem Hagen <i>et al.</i> , 2013	rsfMRI	18 ASD 25 TD	19–40	DMN, salience, and medial temporal lobe networks	Whole brain with ICA and seed-based approaches within and between 3 different networks	X (long-range)	
Cornew <i>et al.</i> , 2012	rsMEG	27 ASD 23 TD	6–15	15 sources in frontal and parietal areas	Whole brain MEG		X (long-range)
Edgar <i>et al.</i> , 2015	rsMEG	41 ASD 47 TD	6–14	Whole brain	Whole brain MEG, with alpha		X (local)
Ghanbari <i>et al.</i> , 2015	rsMEG	26 ASD 22 TD	6–15	Whole cortex	Whole brain MEG, with measures of complexity/connectivity across 6 bands		X (long-range)
Kitzbichler <i>et al.</i> , 2015	rsMEG	15 ASD 15 TD	6–21	Whole cortex	Whole brain MEG, with measure of connectivity and graph theory metrics across 5 bands		X (long-range)
Ye <i>et al.</i> , 2014	rsMEG	16 ASD 15 TD	12–15	90 cortical and subcortical sensors	Phase synchrony estimated between each source pair	X (long-range)	X (long-range)
Ambrosino <i>et al.</i> , 2014	fMRI [EF]	19 ASD 19 TD	9–14	28 networks per age group from ICA (e.g., DMN, visual network)	Between-group connectivity among different networks compared	No differences	No differences
Barbeau <i>et al.</i> , 2015	fMRI [Visual/Spatial]	22 ASD 24 TD	14–38	6 ROIs in bilateral motor and visual cortices	ROI pairwise correlations	X (long-range)	X (long-range)
Deshpande <i>et al.</i> , 2013	fMRI [ToM]	15 ASD 15 TD	16–29	18 ROIs	MVAR model used to assess effective connectivity between ROIs. SVM used to classify participants based on granger path weights	X (long-range)	
Fitzgerald <i>et al.</i> , 2015	fMRI [EF]	21 ASD 21 TD	12–24	DAN and VAN networks	PPI analysis (cue-onset, valid, and invalid trials) between ROIs	X (long-range)	X (long-range)
Keehn <i>et al.</i> , 2013	fMRI [Visual/Spatial]	19 ASD 19 TD	8–18	DAN and VAN networks; visual regions	ROI correlations and ROI-voxel-wise (whole brain) correlations		X (long-range and local)
Libero <i>et al.</i> , 2014	fMRI [Social]	27 ASD 23 TD	13–40	20 ROIs	ICA approach used to identify components. Coherence maps for each subject constructed and compared	X (long-range)	X (local)
McGrath <i>et al.</i> , 2012	fMRI [Visual/Spatial]	22 ASD 22 TD	13–21	6 ROIs (e.g., caudate, IFG)	PPI analysis between seed ROIs and rest of brain	X (long-range)	

Table 1 (Continued)

Citation	Method	N	Age range	ROIs	Approach	Under-Connectivity	Over-Connectivity
McGrath <i>et al.</i> , 2013	fMRI [Visual/Spatial]	22 ASD 22 TD	13–21	6 ROIs	PPI analysis between seed ROIs and rest of brain (also used DTI)	X (long-range)	
Murphy <i>et al.</i> , 2012	fMRI [ToM]	12 ASD 13 TD	Mean 10.4	Right and left amygdala	Whole brain, seed-based PPI approach using amygdala seeds		X (long-range)
Odriozola <i>et al.</i> , 2015	fMRI [ToM]	23 ASD 22 TD	Mean 10.5	Insula	Whole brain, seed-based PPI approach using insular seeds	X (long-range)	X (long-range)
Radulescu <i>et al.</i> , 2013	fMRI [Language]	22 ASD 26 TD	21–47	IFG, insula, caudate, and precuneus	PPI on two conditions and DCM among ROIs		X (long-range)
Sharda <i>et al.</i> , 2014	fMRI [Language]	22 ASD 22 TD	6–16	Left IFG seed	Whole brain, seed-based PPI approach using IFG seed	X (long-range)	X (long-range)
Weisberg <i>et al.</i> , 2014	fMRI [Social]	24 ASD 19 TD	13–23	Right lateral fusiform	Whole brain, seed-based approach using lateral fusiform seed	X (long-range)	
Williams <i>et al.</i> , 2013	fMRI [Language & ToM]	28 ASD 26 TD	Mean 13; 25	8 ROIs (e.g., left IFG, MTG)	Condition specific correlations between pairs of ROIs	X (long-range)	
Khan <i>et al.</i> , 2013	MEG [Social]	17 ASD 20 TD	14–20	FFA and rest of cortex	Whole brain, seed-based event-related coherence between FFA and rest of cortex	X (long-range and local)	
Kikuchi <i>et al.</i> , 2013	MEG [Social]	35 ASD 35 TD	3–7	5 ROIs, 10 connections of interest in each hemisphere	Seed-based with sensor seed in temporal or parietal lobe; assessed intrahemispheric coherence in 9 frequency bands		X (long-range)
Kikuchi <i>et al.</i> , 2015	MEG [Social]	50 ASD 50 TD	3–7	14 pairs of sensors located over anterior and posterior regions	Focus on theta band; examined connectivity between seed sensor in frontal left area and rest of sensors	X (long-range)	
Hanaie <i>et al.</i> , 2014	DTI	18 ASD 12 TD	5–14	Corpus callosum	Tractography – FA, AD, RD	X (long-range)	
Kirkovski <i>et al.</i> , 2015	DTI	25 ASD 24 TD	19–56	Whole brain	TBSS – FA, MD, RD, AD	No differences	No differences
Koldewyn <i>et al.</i> , 2014	DTI	52 ASD 73 TD	Mean 8.88	18 white matter pathways	Tractography – FA, MD, RD, AD	X (long-range)	
McGrath, <i>et al.</i> , 2013	DTI	25 ASD 25 TD	Mean 17.37	IFOF and arcuate fasciculus	HARDI; Tractography – FA, CP, CL	X (long-range)	
Schaer <i>et al.</i> , 2013	DTI	11 ASD 11 TD	9–17	Whole brain	TBSS & Tractography – FA	X (long-range)	
Shukla <i>et al.</i> , 2011	DTI	26 ASD 24 TD	9–20	Whole brain	TBSS – FA, MD, RD, AD	X (long-range)	
Travers <i>et al.</i> , 2015	DTI	100 ASD 56 TD	3–41	Corpus callosum subregions	FA, MD, RD, AD	X (long-range)	
Alaerts <i>et al.</i> , 2014	rsfMRI + Task [Social]	15 ASD 15 TD*	Mean 21.7	Bilateral pSTS	pSTS seed used to correlation with all other voxels	X (long-range)	
Deshpande <i>et al.</i> , 2013	Task + DTI [ToM]	15 ASD 15 TD	16–34	18 social regions	Effective connectivity (MVAR); classification using machine learning with FC + DTI (FA)	(long-range)	
Fishman <i>et al.</i> , 2015	rsfMRI + DTI	35 ASD 35 TD	8–17	14 imitation region seeds; IFG, premotor cortex tracts	Seed-based, voxelwise approach; tractography – FA, MD	X (long-range & local)	X (long-range)

Table 1 (Continued)

Citation	Method	N	Age range	ROIs	Approach	Under-Connectivity	Over-Connectivity
Mueller, et al., 2013	VBM + DTI + rsfMRI	12 ASD 12 TD	Mean 35.5	STS, TPJ, frontal lobe	TBSS, group differences in grey matter, ICA for network selection (rsfMRI), with voxel-wise comparisons in and out of networks	X (long-range)	X (long-range)
Nair et al., 2013	rsfMRI + DTI	29 ASD 34 TD	9–17	5 cortical seeds	Correlation between cortical seeds and thalamus; Tractography	X (long-range)	X (long-range)
Radulescu, et al., 2013	Task + VBM [Language]	22 ASD 26 TD	19–49	IFG, insula, caudate, precuneus	PPI & DCM analysis during 'letter' and 'control' conditions; Whole brain texture analysis of grey matter, regional VBM		X (long-range)
Ray et al., 2014	rsfMRI + DTI	16 ASD 20 ADHD 20 TD	7–13	219 cortical regions	Evaluated "rich-club organization" using graph theory metrics		X (long-range)
You et al., 2013	rsfMRI + Task [EF]	15 ASD 16 TD	9–13	Frontal, temporal, and parietal seeds	Voxel-wise method to capture distal and local connections		X (long-range)

Notes: An 'X' in the under- or over-connectivity columns indicates that the authors reported the presence of this type of connectivity * $N = 15$ in original data set, replication set was 278 ASD and 306 TD from ABIDE; mean age in replication set was 15.9. Mean age is reported when the range was not available.

characterizing aberrant activation within specific cortical and subcortical (especially limbic) regions. This region of interest (ROI) approach has led to core findings about atypical activation in numerous regions, particularly those that are implicated in processing socially relevant stimuli such as faces and their concurrent emotions (e.g. Scherf, Elbich, Minshew & Behrmann, 2015; Weng, Carrasco, Swartz, Wiggins, Kurapati *et al.*, 2011; Whyte, Behrmann, Minshew, Garcia & Scherf, 2016). Approximately 15 years ago, researchers began to evaluate whether there are atypicalities in the *functional interactions* between brain regions in autism. These *functional connectivity* analyses evaluate the temporal synchrony in activation between discrete regions in the brain under the premise that neurons that fire together wire together (Hebb, 1949). The most common methodological approach is to employ correlation analyses to evaluate the strength of the contemporaneous temporal synchrony of response profiles between pairs of regions across the timecourse of the experimental paradigm. Functional connectivity studies in autism have led to findings of reduced coherence (i.e. communication) between some regions in the brain, as revealed by decreased synchronous activation (i.e. correlated signal) between regions (e.g. Just *et al.*, 2004). Researchers have primarily been interested in understanding whether atypical functional connectivity is generally characteristic of autism. However, more recently, given

the developmental nature of the disorder, researchers have begun to ask whether and when developmentally the profile of functional connectivity becomes disrupted in autism (Uddin, Supekar & Menon, 2013). In this way, measures of functional connectivity may have the potential to serve as powerful tools for understanding the etiology and developmental course of autism.

There are multiple ways to quantify neural connectivity. A primary distinction is between functional (activation) and structural (physical) connections. As described above, *functional connectivity* (FC) is the temporal synchrony in functional activation between neural regions, which is typically measured by comparing timeseries data via correlation. Importantly, measures of FC are agnostic regarding the causality or direction of the connection. In contrast, measures of *effective connectivity* (EC) do involve estimating directed connections between regions and require the use of measures, like granger causality, unified SEM, dynamic casual modeling. This is a critical difference between the two kinds of connectivity measures that has important implications for characterizing and quantifying network organization and topological structure.

In addition to understanding the statistical approaches used to compute measures of connectivity, it is important to understand what participants are doing while the data are being acquired that will be used to estimate neural connectivity. *Resting-state fMRI connectivity* (rsfMRI) is

functional connectivity that exists in the absence of specific task demands (Biswal, Zerrin Yetkin, Haughton & Hyde, 1995). Participants are asked to lie still in the scanner, usually with their eyes open, for a period of 5 minutes or more while they are scanned. Neural connectivity acquired under these conditions is thought to reflect a life history of Hebbian learning between neurons (Biswal *et al.*, 1995). Historically, rsfMRI is almost always analyzed using FC, not EC statistical methods. In contrast, *task-based connectivity* is analyzed from paradigms in which participants are performing an explicit task, and therefore is modulated by the particular task. Task-based connectivity will engage more specific networks depending on the task demands, and therefore requires careful attention to the selection of the nodes from which the timeseries are pulled. This approach could be used to evaluate the prediction that FC in autism could be disrupted in a task-specific way that is related to behavioral symptoms, and not in a ubiquitous way.

In the autism literature, because of the emphasis on Belmonte's and Just's frameworks, patterns of connectivity are generally described in terms of *under-connectivity* (e.g. smaller/weaker correlations between regions, or reduced correlations in a sample with autism compared to controls) or *over-connectivity* (e.g. larger/stronger correlations between regions, or heightened correlations in a sample with autism compared to controls). Some studies also report *positive* and/or *negative* connectivity, which is not to be confused with under- or over-connectivity. That is, *positive connectivity* occurs when activity increases in one brain region while activity also increases in the other correlated brain region (i.e. a positive correlation between regions). In comparison, *negative connectivity* occurs when activity increases or decreases in one region while tending to decrease simultaneously in another (i.e. a negative correlation between regions). Finally, we also review work on *structural connectivity*, which includes methodologies used to assay the micro- and macro-structural properties of white matter tracts (e.g. DTI or fiber tracking, volumetric analyses) or grey matter (e.g. VBM) within the brain.

While considering the evidence, it is also important to note that although Belmonte and colleagues (2004) distinguished local and long-range connectivity, they did not provide a specific definition for either kind of connection, except to say that local connections are within 'neural assemblies' and long-range connections are 'between functional regions'. Unfortunately, this definition makes it very difficult to evaluate whether evidence supports or fails to support the argument that Belmonte and colleagues provided about atypical brain organization in autism. As a result, the field has been

quite liberal when interpreting these concepts. Some researchers have attempted to operationally define the distance of connections in previous reviews of the literature. For example, Vissers and colleagues (2012) defined short-range connections as those contained within 1 cm^3 and long-range connections to be outside this range. However, this definition may not capture the notion of 'neural assemblies' in the way Belmonte and colleagues suggested given that neurons assemble in minicolumns and cortical layers, neither of which are measurable at the resolution of functional neuroimaging. The smallest resolution of fMRI data is the voxel, in which an estimated 630,000 neurons assemble (in a typical 3 mm^3 voxel – 2.1×10^9 of which would be in 1 cm^3), but connectivity cannot be measured within a single voxel. Structural connections can be measured between voxels, but functional connections are typically measured between functional *regions*. As a result, in this review we characterize findings as the authors of the papers do instead of creating our own definition.

Resting-state connectivity using fMRI

The use of resting-state connectivity methods has become a burgeoning area of research in understanding the neural underpinnings of autism. Resting-state fMRI (rsfMRI) measures coherent spontaneous low-frequency oscillations in the blood oxygenation level dependent (BOLD) signal between pairs of neural regions in the absence of any specific task performance (Fox & Raichle, 2007; Biswal *et al.*, 1995). These patterns of spatial coherence are believed to represent stable intrinsic functional organization of neural networks. Here, we review the most recent and methodologically rigorous studies using resting-state techniques that tested large samples of individuals with autism, including several studies using data from the Autism Brain Imaging Data Exchange (ABIDE) (Alaerts, Di Martino, Swinnen & Wenderoth, 2013; Abrams, Lynch, Cheng, Phillips, Supekar *et al.*, 2013; Anderson, Nielsen, Froehlich, DuBray, Druzgal *et al.*, 2011; Bos, van Raalten, Oranje, Smits, Kobussen *et al.*, 2014; Di Martino *et al.*, 2014; Domínguez, Velázquez & Galán, 2013; Gotts, Simmons, Milbury, Wallace, Cox *et al.*, 2012; Keown, Shih, Nair, Peterson, Mulvey *et al.*, 2013; Lynch, Uddin, Supekar, Khouzam, Phillips *et al.*, 2013; Nair, Treiber, Shukla, Shih & Müller, 2013; Nomi & Uddin, 2015; Maximo, Keown, Nair & Müller, 2013; You, Norr, Murphy, Kuschner, Bal *et al.*, 2013).

Long-range functional connectivity differences

Resting-state studies have focused on both long-range inter-regional connectivity as well as relatively

shorter-range local connectivity, as measured by correlations involving methods such as Regional Homogeneity or 'ReHo' (Zang, Jiang, Lu, He & Tian, 2004; see Maximo *et al.*, 2013, for review/discussion). Initial studies typically employed relatively small sample sizes (e.g. < 20 per group) and focused on seed-based correlations with a small number of seed regions, such as the posterior cingulate cortex used to identify the 'default mode network' (e.g. Monk, Peltier, Wiggins, Weng, Carrasco *et al.*, 2009; see also Ebisch, Gallese, Willems, Mantini, Groen *et al.*, 2011). Many of these studies reported reduced functional connectivity in individuals with autism relative to TD controls throughout the cortex, with a few documenting over-connectivity for subcortical-cortical interactions (e.g. using seeds in the striatum, Di Martino, Kelly, Grzadzinski, Zuo, Mennes *et al.*, 2011; also see later studies by Cerliani, Mennes, Thomas, Di Martino, Thioux *et al.*, 2015; Delmonte, Gallagher, O'Hanlon, McGrath & Balsters, 2013; Padmanabhan, Lynn, Foran, Luna & O'Hearn, 2013). Anderson and colleagues published the first whole-brain search for group differences in larger groups (40/group) by using more than 7000 seed regions sampled throughout the gray matter (Anderson *et al.*, 2011). These authors controlled for multiple comparisons through permutation testing and found decreased long-range functional connectivity involving the bilateral medial prefrontal, posterior cingulate, ventral temporal and insular cortex, as well as the STS and intraparietal sulcus in the autism group.

In 2012, two prominent rsfMRI connectivity papers highlighted the role that measurement artifacts, such as transient head motion, can play in the detection of group differences (e.g. Power *et al.*, 2012; van Dijk *et al.*, 2012). As a result, papers published after this work exerted more effort to examine motion and other global artifacts in rsfMRI studies. For example, Gotts and colleagues conducted a rsfMRI study in which they used the whole-brain average correlation measures to empirically detect effective seeds that elicited group differences, which were then tested to gain a more complete picture of the functional connectivity differences (Gotts *et al.*, 2012). Similar to the Anderson *et al.* (2011) study, they found that the strongest group differences involved regions of the 'social brain' (e.g. Adolphs, 2009; Frith & Frith, 2007; Mitchell, 2009; Olson, Plotzker & Ezzyat, 2007), with decreased functional connectivity in autism involving the ventromedial prefrontal cortex, temporal polar regions, STS/STG, amygdala, hippocampus, ventral temporal cortex, and the inferior frontal gyrus, as well as somatosensory, supplementary motor, and intraparietal cortex (see also von dem Hagen, Stoyanova, Baron-Cohen & Calder, 2013). When they censored high

motion time points in order to match transient motion between the autism and control groups, these differences remained. Of note, this study also observed that correlations with symptom severity in the autism group (as measured on the Social Responsiveness Scale) mirrored the pattern of group differences in terms of the detailed region-by-region pattern. Tyszka and colleagues (2014) also found a similar but weaker pattern of group differences between motion-matched autism and control groups who were compared using a large set of regions of interest covering much of the brain. These researchers reported largely similar patterns of connectivity in autism and control groups, although they also observed reduced functional connectivity between frontal and temporal regions in the autism group (Tyszka, Kennedy, Paul & Adolphs, 2014).

In contrast, at least two other studies have reported evidence of *increased* long-range functional connectivity in autism, or combinations of increases and decreases in functional connectivity depending on the location (e.g. Chien, Lin, Lai, Gau & Tseng, 2015; Rudie, Brown, Beck-Pancer, Hernandez, Dennis *et al.*, 2013). These seemingly conflicting reports have raised questions as to whether group differences in rsfMRI between autism and TD groups are replicable and reliable, or whether results vary systematically as a function of methodological choices in data preprocessing (see Gotts Saad, Jo, Wallace, Cox *et al.*, 2013; Hahamy, Behrmann & Malach, 2015; Nair, Keown, Datko, Shih, Keehn *et al.*, 2014, for further discussion).

Large multi-site data-sharing initiatives such as ABIDE have had a large impact on these questions, permitting tests of replication and of the impact of preprocessing variables on observed results. The overview ABIDE paper itself (Di Martino *et al.*, 2014), reported the analysis of 112 seed regions in 360 autism and 403 control participants. The researchers reported that long-range cortico-cortical resting-state functional connectivity was predominantly decreased in autism, consistent with most of the prior reports discussed above, with *increased* functional connectivity between subcortical (e.g. thalamus and globus pallidus) and cortical regions (e.g. sensorimotor and parietal regions). Similarly, a more extensive approach was used on the same dataset that included 418 autism, 509 matched controls from 16 sites and that involved a comprehensive search for long-range group differences over all possible voxel combinations, correcting for multiple comparisons (via False Discovery Rate, FDR) and motion magnitude (via mean Framewise Displacement), and included a replication analysis across two independent subsets of the data (Cheng, Rolls, Zhang & Feng, 2015). The researchers observed decreased long-range functional

connectivity in the autism group in medial prefrontal, posterior cingulate, bilateral STS/MTG, and bilateral sensorimotor cortex, along with increased functional connectivity in the medial thalamus, right SMA, left STS, and superior frontal gyrus. Finally, Hahamy and colleagues (2015), also using ABIDE data (68 autism, 73 control participants), examined group differences in patterns of intra- and inter-hemispheric functional connectivity. Similar to Dinstein, Heeger, Lorenzi, Minshew, Malach *et al.* (2012), they reported more variable, idiosyncratic patterns of both increased and decreased connectivity in individual autism participants that replicated across separate ABIDE sites and predicted the severity of social symptoms across participants (for commentary, see Uddin, 2015).

Taken together, these recent findings on long-range functional connectivity differences between autism and control hold together quite well with a number of the previously reported findings (e.g. Anderson *et al.*, 2011; Di Martino *et al.*, 2011; Monk *et al.*, 2009) and converge to suggest a pattern of cortico-cortical under-connectivity, particularly among regions implicated in aspects of social processing, and subcortical-cortical over-connectivity in resting-state connectivity in autism.

Local functional connectivity differences

Critical for the Belmonte *et al.* hypothesis is whether the regions showing reliable long-range group differences in functional connectivity also show the reversed pattern locally, with greater local functional connectivity in autism. Despite examination of the issue in several studies, there has been little supporting evidence for this hypothesis, with most studies offering contrary evidence or a lack of a relationship. For example, Gotts *et al.* (2013) directly examined the average functional connectivity within each area showing long-range connectivity differences between autism and control groups. Under the preprocessing pipeline that obtained significant agreement between group differences and symptom correlations within the autism group, 6 out of 27 regions examined showed significantly *reduced* rather than enhanced local connectivity in the autism group, with no region showing significant effects in accord with the Belmonte *et al.* prediction. Other studies have examined local correlations systematically over the whole brain using techniques such as ReHo, based on Kendall's coefficient of concordance among adjacent voxel time-series within a local sphere. For example, Maximo and colleagues (2013) found increases in local connectivity in autism in occipital and posterior ventral temporal regions, along with decreased local connectivity in posterior/middle cingulate and medial prefrontal cortex.

In contrast, in the much larger sample described in the overview ABIDE paper (Di Martino *et al.*, 2014), the autism group exhibited local connectivity increases in right medial and superior frontal cortex, along with decreased local correlations in the posterior cingulate cortex, left insula and thalamus, with no changes observed in occipitotemporal regions. Critically, these changes bore little resemblance to the long-range correlation differences observed in the same subjects (discussed above), indicating no evidence of a systematic relationship between increased local correlations and decreased long-range correlations.

Resting-state connectivity using MEG

While many more studies have examined altered resting-state functional connectivity in autism using fMRI, a growing number of studies have employed magnetoencephalography, or MEG. MEG provides improved spatial resolution over EEG, while allowing high temporal resolution on the order of a millisecond. As mentioned earlier, the difficulty of adjudicating changes in functional connectivity between two spatially separate estimated sources in EEG and a change in power in a single source (see Ghuman *et al.*, 2011, for further discussion) has led us to restrict our review of articles to MEG for the current paper because of its superior spatial resolution.

Long-range functional connectivity differences

The first whole-brain MEG study of resting-state functional connectivity in autism carried out in source-localized data (using a scalar beamformer technique) was conducted by Ye, Leung, Schäfer, Taylor and Doesburg (2014). In this study of adolescents with and without autism, the researchers first filtered the source-estimated data into bands (delta: 1–4 Hz, theta: 4–7 Hz, alpha: 8–14, beta: 15–30 Hz, gamma: 30–80 Hz, and high gamma: 80–150 Hz) and then calculated the weighted Phase Locking Index (wPLI), which is a form of phase synchrony that has improved robustness to the field spreading and volume conduction problems discussed by Ghuman *et al.* (2011). Ye *et al.* observed greater long-range phase-locking in participants with autism among frontal, temporal, and subcortical regions in both the beta and gamma frequencies, as well as decreased phase-locking among occipital and parietal regions with much of the brain in theta and alpha frequencies.

Kitzbichler, Khan, Ganesan, Vangel, Herbert *et al.* (2014) conducted a similar study in individuals with autism and TD individuals across a broad age span (6–21), with a larger emphasis on a graph theoretical

approach. Like Ye *et al.* (2014), they found increased correlation in gamma frequencies in participants with autism involving frontal, temporal, parietal, and occipital regions. However, they found a reversed pattern of results for beta frequencies (TD>autism) relative to Ye *et al.*, as well as in alpha (autism>TD) involving similar regions. Indeed, the overall pattern of results was quite complex, finding group differences across all frequency bands examined, in multiple networks and sub-networks, and in most graph theoretic measures tested. Critically, though, correlations in beta and gamma frequencies among multiple combinations of sub-networks predicted the severity of autism symptoms as measured by the ADOS.

One additional MEG study examined measures of functional connectivity across the same range of frequencies. Ghanbari, Bloy, Edgar, Blaskey, Verma *et al.* (2015) measured resting-state data in children and adolescents with and without autism, evaluating overall signal complexity (i.e. sample entropy) as a measure of functional connectivity (lower signal complexity → higher functional connectivity) for different frequency bands. Participants with autism exhibited lower signal complexity (i.e. greater rhythmicity, less randomness) in the delta band in sensors near frontal cortex and in the alpha band in sensors near occipital and parietal cortex. At the same time, they also exhibited higher signal complexity (i.e. reduced rhythmicity, more randomness) in the delta band for sensors over parietal cortex, in the theta band for sensors over parietal and temporal cortex, and in the gamma band near frontal midline sensors. Interestingly, greater connectivity in the delta frequencies involving sensors over frontal, temporal, and parietal regions predicted higher autism symptoms as measured by the SRS total score.

In sum, these MEG studies do not support a simple pattern of decreased long-range functional connectivity. All three of these studies found evidence of greater long-range connectivity for certain frequencies, and Ye *et al.* and Kitzbichler *et al.* both found mixed patterns of results, although it should be noted that the pattern of results was quite variable from study to study.

Local functional connectivity differences

The measure from MEG that is most relevant to the question of local functional connectivity is source-estimated signal power for a given frequency band. When local signals are more synchronized, this will be reflected as greater common fluctuations in the magnetic field, which corresponds to greater power (a measure of the variance of the signal). Two recent MEG resting-state studies examined signal power in participants with

autism and TD participants in source-estimated data. Cornew, Roberts, Blaskey and Edgar (2012) studied local power differences in source-estimated MEG data in children and adolescents with and without autism. In absolute power, they observed increases in those with autism for theta and alpha frequencies in parietal, temporal, and occipital sources. When examining relative power (band-limited power divided by total power), they observed increases in delta (frontal sources) and alpha frequencies (lateral anterior temporal near the STS and occipito-parietal sources) in participants with autism, with increased alpha power at these sites predicting greater social impairment. Similarly, Edgar, Heiken, Chen, Herrington, Chow *et al.* (2015) found greater relative alpha power for children and adolescents with autism in left parietal regions that also predicted higher SRS scores. Both studies suggest that alpha power in parietal and temporal sites is elevated in autism, and that these increases are related to the social symptoms that are central to the disorder.

While this pattern is partially consistent with the Belmonte *et al.* proposal of increased local connectivity, the long-range functional connectivity results of Ye *et al.* (2014) and Kitzbichler *et al.* (2014) both support a mixed pattern of increased and decreased connectivity across different frequency bands. Finally, the Ghanbari *et al.* (2015) study stands in contrast to predictions from both models in the findings of increased long-range connectivity in the delta frequency that predicts social symptoms. Overall, these MEG studies establish a complex pattern of increased local power and both increased and decreased long-range functional connectivity that does not provide straightforward support for either the Just *et al.* or Belmonte *et al.* proposals.

Conclusions from resting-state connectivity literature

The bulk of evidence, particularly from the most rigorous and well-powered of the rsfMRI studies, is inconsistent with the central hypothesis of pervasive under-connectivity of autism as originally articulated by Just *et al.* (2004). Although there is converging evidence of under-connectivity in connections with temporal, medial and lateral frontal, and somatosensory cortex, there are many findings of *increased* correlation, or over-connectivity, particularly in subcortical-cortical connections involving the thalamus, striatum, and other portions of the basal ganglia, which has been observed across multiple studies. Similarly, this set of results is also markedly inconsistent with the hypotheses put forth in the Belmonte *et al.* (2004) paper about complementary local and long-distance connectivity abnormalities in autism, both in fMRI and MEG.

Task-based connectivity using fMRI

In contrast to rsfMRI, task-based functional connectivity is assessed as participants are engaged in a particular task. Findings from these studies describe the functional organization among nodes of a neural network under different task conditions. As a result, in reviewing this literature, we note that task-related studies generally fall within one of four task domains: language (Jones, Bandettini, Kenworthy, Case, Milleville *et al.*, 2010; Just *et al.*, 2004; Radulescu, Minati, Ganeshan, Harrison, Gray *et al.*, 2013; Sharda, Midha, Malik, Mukerji & Singh, 2015; Williams, Cherkassky, Mason, Keller, Minshew *et al.*, 2013), Theory of Mind (ToM)/ social information processing (Deshpande, Libero, Sreenivasan, Deshpande & Kana, 2013; Libero, Stevens & Kana, 2014; Murphy, Foss-Feig, Kenworthy, Gaillard & Vaidya, 2012; Odriozola, Uddin, Lynch, Kochalka, Chen *et al.*, 2015; Weisberg, Milleville, Kenworthy, Wallace, Gotts *et al.*, 2014), executive functioning (Ambrosino, Bos, van Raalten, Kobussen, van Belle *et al.*, 2014; Fitzgerald, Johnson, Kehoe, Bokde, Garavan *et al.*, 2014), and visual and spatial processing (Barbeau, Lewis, Doyon, Benali, Zeffiro *et al.*, 2015; Keehn, Shih, Brenner, Townsend & Müller, 2013; McGrath, Johnson, Ecker, O'Hanlon, Gill *et al.*, 2012; McGrath, Johnson, O'Hanlon, Garavan, Gallagher *et al.*, 2013). As such, we review each of the four task domains.

In the language domain, only one other study that meets our inclusion criteria converges with the original under-connectivity finding reported by Just and colleagues (2004) and it is another study by this same group (Williams *et al.*, 2013). While reading brief literal and ironic stories, children and adults with autism exhibited reduced functional connectivity, specifically during the irony condition, within a left hemisphere language network, but not in the right hemisphere theory of mind network, compared to their respective age- and ability-matched comparison groups. Aside from this study, there are no other studies meeting our selection criteria within the language domain that converge with Just's original findings.

In comparison, another study reported over-connectivity in individuals with autism while they engage in a verbal fluency task. In particular, adults with autism evinced stronger connectivity between the caudate nucleus and the insula and superior frontal gyrus than controls (Radulescu *et al.*, 2013). Other work has shown that results are highly dependent upon condition or task demands within the language domain. Specifically, one study in which children and adolescents with autism passively listened to sung words, spoken words, and piano tones, conducted a PPI connectivity analysis

on each condition using a left IFG seed (Sharda *et al.*, 2015). During the sung words condition, the autism group exhibited over-connectivity between the IFG and cerebellum compared to the TD group. In contrast, during the spoken word condition, the autism group exhibited under-connectivity between the IFG and a left temporal region compared to the TD group. Together, findings from these language studies show no consistency across study with respect to patterns of under-connectivity during language processing in autism.

In studies of social information processing in individuals with autism the neural connectivity findings are also quite mixed. These studies typically gauge social information processing using face-processing tasks. In these studies, there are some reports of under-connectivity between the lateral fusiform and the STS and amygdala (e.g. Weisberg *et al.*, 2014). However, others report *stronger* connectivity between regions of the face-processing network (i.e. amygdala) and the IFG (as well as posterior and dorsal cingulate, STS, thalamus, and insula) (Murphy *et al.*, 2012).

The theory of mind (ToM) studies typically employ tasks in which participants make attributions about the goals or intentions of characters in situational vignettes (Deshpande *et al.*, 2013; Kana, Uddin, Kenet, Chugani & Müller, 2014) or based on their body position (Libero *et al.*, 2014). Findings from these studies are a bit more convergent. That is, studies using ToM paradigms tend to report weak connectivity between temporal regions in autism (Deshpande *et al.*, 2013; Libero *et al.*, 2014, Lombardo, Chakrabarti, Bullmore, Sadek, Pasco *et al.*, 2010). For example, one study reported weaker connectivity between the right lateral fusiform (including the FFA) and the right pSTS and amygdala in autism participants compared to controls while viewing social vignettes involving abstract geometric shapes (Weisberg *et al.*, 2014). By and large, these findings suggest that perhaps the temporal lobe is a particularly vulnerable area during ToM processing for individuals with autism. This is unsurprising given that the temporal lobe supports many aspects of social information processing, which is problematic for individuals with autism. However, at least one study found no differences in the ToM networks between children and adults with autism and age-matched controls (Williams *et al.*, 2013).

To our knowledge, only two studies have investigated the functional connectivity patterns implicated in executive functioning in autism (Ambrosino *et al.*, 2014; Fitzgerald *et al.*, 2015). Ambrosino and colleagues (2014) used a data-driven ICA connectivity approach to investigate cognitive control in a sample of children

and adolescents with and without autism. When performing a go/no-go task with Pokémon characters, there were no reported connectivity differences between the two groups (Ambrosino *et al.*, 2014). Another study examined connectivity differences among adolescents and adults with and without autism in the ventral attention network (i.e. involuntary attention in a reflexive manner to unanticipated stimulus) and the dorsal attention network (i.e. voluntary, goal-driven attention) during a Posner-cueing task (Fitzgerald *et al.*, 2015). Within the dorsal attention network (i.e. frontal eye field, intraparietal sulcus) the individuals with autism had weaker functional connectivity compared to controls. In the ventral attention network (i.e. temporoparietal junction, frontal operculum, middle and inferior frontal gyri, and the anterior insula) the group with autism demonstrated positive functional connectivity while the control group evinced negativity connectivity. The authors of this study interpret these findings to reveal that the neural dynamics of behavioral deficits in autism are disproportionately related to engaging in behaviors that require goal-driven attention.

In the few visual and spatial task-related functional connectivity studies that exist, findings of both distal over- and under-connectivity in adolescents/adults with autism have been reported (Keehn *et al.*, 2013; McGrath *et al.*, 2012; McGrath *et al.*, 2013). We highlight this domain because it is one that has been identified as eliciting superior performance in individuals with autism (Kaldy, Krapar, Carter & Blaser, 2011) and has been related to core social impairments that characterize the disorder (Joseph, Keehn, Connolly, Wolfe & Horowitz, 2009). In one study using a visual search task, children and adolescents with autism showed over-connectivity within and between attention networks compared to TD controls (Keehn *et al.*, 2013). In addition, both local connections within visual cortex and distal connections between visual and frontal regions exhibited over-connectivity in the autism group. In more complex visuospatial tasks, like those involving mental rotation, findings have been highly inconsistent. For example, in one mental rotation study, adolescents and adults with autism showed under-connectivity compared to controls as task demands increased (McGrath *et al.*, 2012). The participants with autism exhibited hyper-negative functional connectivity between a BA19 seed region in visual cortex and left IFG, as well as hypo-negative connectivity between BA19 and MFG in comparison to controls. The authors of this study interpret these results to indicate that there is widespread underconnectivity in autism when accomplishing a mental rotation task. Another study using the same mental rotation task revealed a similarly complicated set of results (McGrath

et al., 2013). That is, findings demonstrated that the participants with autism had reduced functional connectivity relative to controls between the thalamus and BA19, as well as the caudate head and BA19. However, there was also evidence of long-range over-connectivity between the left caudate body and BA19. By and large, these findings are discouraging in terms of drawing any conclusions regarding the nature of connectivity even during the same visuospatial task.

Taken together, the task-based fMRI functional connectivity findings do not converge within or across domains. In each domain, there are reports of both relatively stronger and weaker long-range functional connections in people with autism compared to typically developing controls. Unlike the rsfMRI studies, there is little to no emphasis on evaluating local-level connections in the task-based connectivity studies using fMRI.

Task-based connectivity using MEG

Relatively few task-based functional connectivity studies have been conducted in MEG that meet our inclusion criteria, and fewer types of tasks have been examined than in studies using fMRI. Researchers have employed passive viewing of videos (Kikuchi, Yoshimura, Shitamichi, Ueno, Hirose *et al.*, 2013; Kikuchi, Yoshimura, Mutou & Minabe, 2015), and of faces and houses (Khan, Gramfort, Shetty, Kitzbichler, Ganesan *et al.*, 2013). Kikuchi *et al.* (2013) examined long-range functional connectivity (coherence) using a custom-MEG system designed for children. Among children who passively viewed engaging videos (chosen by each child), there were no differences in local power at any of the sensors, but there was greater gamma band coherence between right parietal and temporal sensor locations in the children with autism. In a subsequent study with a larger sample using the same task, Kikuchi *et al.* (2015) found reduced theta coherence between left anterior and right posterior source locations in the children with autism, that predicted ADOS total scores.

In another study examining the relationship between local and long-range functional connectivity in individuals with autism, Khan *et al.* (2013) asked adolescents and adults to view pictures of fearful, angry and neutral faces, as well as pictures of houses. As a measure of long-range functional connectivity, they calculated event-related coherence between the FFA and the rest of the brain. Reduced alpha coherence was observed in participants with autism between the FFA and the left precuneus, the left inferior frontal gyrus, and the left anterior cingulate cortex during the viewing of faces. While no group differences were observed in local power during any viewing conditions, they observed reduced

local phase-amplitude coupling in participants with autism between alpha and gamma frequencies in the FFA during face viewing (i.e. gamma power was less modulated by the phase of alpha). Khan and colleagues interpreted this finding to reflect reduced local functional connectivity in the group with autism. Reduced local phase-amplitude coupling in the FFA corresponded with reductions in long-range alpha coherence from the FFA in both groups (significant correlations in both groups). This reduced alpha-gamma phase-amplitude coupling also predicted higher ADOS social scores for participants with autism. When combining short- and long-range measures of connectivity, autism versus typical status could also be classified with 90% accuracy. These findings strongly contradict the Belmonte *et al.* proposal by revealing both reduced local and increased long-range functional connectivity (see also Gotts *et al.*, 2013).

Conclusions from task-based connectivity literature

Neither the fMRI nor the MEG task-based studies converge to support the hypotheses of local over-connectivity and distal under-connectivity in the autism participants. In fact, in some studies, the opposite patterns were uncovered (e.g. increased distal, decreased local connectivity) (e.g. Khan *et al.*, 2013; Keehn *et al.*, 2013; Sharda *et al.*, 2015), which directly contradicts the predictions set forth by Belmonte *et al.* and Just *et al.* Moreover, some studies have failed to find any differences in local or distal connectivity between individuals with autism and TD individuals as a function of task demands (e.g. visual search – Keehn *et al.*, 2013; language – Williams *et al.*, 2013). Therefore, we suggest that the existing data are more easily understood in terms of the task demands, symptom severity, developmental period, and with consideration for the role of specific neural regions and networks. For this reason, we encourage future work to focus on more developmentally appropriate task-modulated connectivity approaches in order to capture how particularly vulnerable networks in autism may be more or less aberrant based on specific task demands.

Structural connectivity

In this section, we evaluate whether findings from structural imaging studies are consistent with either of the Just *et al.* or Belmonte *et al.* hypotheses about brain organization in autism. In the most recent studies using structural connectivity methodologies (i.e. Diffusion Tensor Imaging (DTI)), there is virtually no evidence in support of *stronger* structural connectivity in autism

populations (Kirkovski, Enticott, Maller, Rossell & Fitzgerald, 2015; Koldewyn, Yendiki, Weigelt, Gweon, Julian *et al.*, 2014; Schaer, Ottet, Scariati, Dukes, Franchini *et al.*, 2013; Shukla, Keehn & Müller, 2011). In other words, no studies to date have reported higher microstructural (functional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), axial diffusivity (AD)) or macrostructural (tract volume) properties in individuals with autism compared to TD controls (but see Ray, Miller, Karalunas, Robertson, Grayson *et al.*, 2014). In contrast, the most consistent finding in these studies is *reduced* microstructural properties of the white matter tracts and volume of the corpus callosum (Hanaie, Mohri, Kagitani-Shimono, Tachibana, Matsuzaki *et al.*, 2014; Schaer *et al.*, 2013; Shukla *et al.*, 2011; Travers, Tromp, Adluru, Lange, Destiche *et al.*, 2015). Other converging structural connectivity findings include reduced microstructural properties of the inferior fronto-occipital fasciculus (IFOF) (McGrath *et al.*, 2013) and the inferior longitudinal fasciculus (ILF) (Koldewyn *et al.*, 2014) in individuals with autism, which are two long-range fiber tracts that originate within the occipital lobe and traverse the temporal lobe, with the ILF terminating in the anterior temporal lobe and the IFOF terminating in the frontal lobe. In one study using targeted tractography protocols, researchers found that the microstructural properties of the IFOF were altered in participants with autism compared to TD participants and that this alteration was linked to behavioral visuoperceptual skills (McGrath *et al.*, 2013). In another study using whole-brain analyses, the same temporal lobe fiber tracts were identified as having weak microstructural properties in autism (Lee, Bigler, Alexander, Lazar, DuBray *et al.*, 2007). Notably, Koldewyn and colleagues found that when data quality is matched between TDs and individuals with autism, the ILF is the *only* tract in the brain that shows microstructural decrements in children with autism, suggesting more similarities than differences between autism and control individuals (Koldewyn *et al.*, 2014). These findings, together with the corpus callosum findings, are among the most compelling results to date that support the notion of aberrant microstructural properties in long-range fiber tracts, particularly those supporting inter- and intra-hemispheric communication in individuals with autism compared to TD individuals.

Multimodal imaging studies

In evaluating the resting-state, task-based, and structural connectivity literatures separately, it is important to consider how these methodologies inform each other when combined in multimodal studies. In this section, we focus on studies that integrate some combination of

these connectivity methodologies to evaluate aberrant patterns of connectivity in autism. First, we look to studies that integrate resting-state and task-based connectivity methodologies in the same participants (Alaerts, Woolley, Steyaert, Di Martino, Swinnen *et al.*, 2014; You *et al.*, 2013). Interestingly, of the two studies that do so, one study finds evidence of converging under-connectivity in autism (Alaerts *et al.*, 2014), while the other reports convergent widespread over-connectivity (You *et al.*, 2013). Specifically, in adults with autism, Alaerts and colleagues report under-connectivity between bilateral pSTS and fronto-parietal regions in both resting-state and task-based functional connectivity (Alaerts *et al.*, 2014). This finding was replicated in two independent samples, one of which was from ABIDE. Conversely, using a voxel-wise method to capture distal and local connections, You and colleagues found that children with autism had increased distal connectivity between frontal, temporal, and parietal regions compared to controls, during the task relative to resting-state (You *et al.*, 2013). Of note, these studies are difficult to compare, given that they examined different age groups (i.e. children and adults) that represent different developmental stages (see Uddin *et al.*, 2013). Though these findings do not corroborate each other, they do reflect that combining resting-state and task-based methodologies to compare connectivity patterns within the same individuals may converge on similar patterns of findings.

Recently, significant advances have been made in the integration of data from multiple imaging modalities in an effort to understand whether there is convergence of atypical functional and structural connectivity in autism. Among the few multimodal studies that exist, there is consensus in their reports of functional and structural atypicalities in the temporal lobe and in motor regions (Deshpande *et al.*, 2013; Mueller, Keeser, Samson, Kirsch, Blautzik *et al.*, 2013; Nair *et al.*, 2013; Radulescu *et al.*, 2013). In general, these studies report weaker functional and structural connections among individuals with autism compared to TD controls. Importantly, these findings only hold when researchers examine properties of functional and structural connectivity within the same individual; otherwise the patterns of findings across the two methods often fail to converge. For example, one study used DTI and functional network analyses to evaluate the existence of group differences in connectivity (Mueller *et al.*, 2013). Using this multimodal approach, Mueller and colleagues demonstrated that individuals with autism have reduced functional and structural connectivity among regions within the default mode network (i.e. medial and superior regions of the frontal cortex, PCC, and parahippocampal gyrus), the dorsal attention network,

and the fronto-parietal network compared to TDs. However, in another multimodal study from the same group, they report pervasive structural hypo-connectivity in the face of mixed findings regarding resting-state functional connectivity (Fishman, Datko, Cabrera, Carper & Müller, 2015). While left inferior frontal gyrus and premotor cortex yielded clusters of greater functional connectivity in the autism participants, the left inferior parietal lobe, right medial premotor cortex, and bilateral lateral occipital cortices yielded clusters of weaker functional connectivity. Perhaps most surprisingly, there were single regions from which patterns of both over- and under-connectivity clusters originated, including the right fusiform face area. These findings challenge the notion of distance as a primary mechanism for determining the atypical neural networks in autism.

Other multimodal studies have reported functional connectivity patterns that are inversely related to (i.e. not at all convergent with) structural connectivity patterns results in autism populations (Nair *et al.*, 2013). For example, Nair and colleagues (2013) found that children and adolescents with autism showed increased functional connectivity coupled with decreased structural connectivity in temporal-thalamic connections. These findings reflect the notion that functional and structural connectivity do not necessarily exhibit a 1:1 correspondence. In this case, the pattern of effects is diametrically opposed, indicating hyper functional connectivity and hypo structural connectivity in the 'same' pathways, which is difficult to interpret. Critically, these findings undermine the notion of structural over-connectivity (local or otherwise) in individuals with autism, contrary to what Belmonte and colleagues (2004) hypothesized.

We would like to highlight a recent multi-modal study that approached studying atypical connectivity in autism in ways not predicted by these early over/under-connectivity hypotheses. Ray and colleagues examined functional and structural connectivity in autism, ADHD, and TD children by evaluating 'rich-club organization' using graph theory metrics (Ray *et al.*, 2014). Rich-club organization reflects network systems that are organized around highly connected nodes, which are connected to other highly connected nodes. Previous work suggests that the human brain shows rich-club organization in its structural connections (van den Heuvel & Sporns, 2011). The researchers asked whether the rich-club organization in resting-state functional and structural networks differed in autism compared to typical brains. Importantly, these researchers used a high dimension reconstruction algorithm (HARDI) for the diffusion data that does not rely on a tensor model and, therefore, circumvents methodological problems like crossing fibers that were problematic for all previous

studies. The researchers assessed functional and structural networks both inside and outside the rich-club organization. They reported that, like TD children, those with autism do exhibit rich-club organization in both their functional and structural neural networks. Furthermore, within both the functional and structural networks, children with autism actually exhibited hyper-connectivity (i.e. more connections) among the nodes within their rich-club networks compared to TD children. This is the only study to date suggesting any degree of structural over-connectivity in individuals with autism. Importantly, the authors note that compared to controls, the children with autism had similar microstructural properties (i.e. FA values) in the structural tracts. In other words, the hyper-connectivity was related to an abundance of connections. The approach used in this study and its conclusions lead to a different characterization of the organizational properties of connectivity in autism that does not converge with (1) findings of weaker structural connectivity, or (2) studies that have used similar graph theory metrics to characterize resting-state functional network topologies and organization (e.g. Itahashi, Yamada, Watanabe, Nakamura, Jimbo *et al.*, 2014). However, this work makes an important contribution to this literature by conceptualizing aberrant connectivity in an entirely different way than as a function of distance (i.e. inside and outside of rich-club hubs). It also provides the first evidence of structural over-connectivity in autism.

Conclusions from the review

It is clear from our review of the most methodologically rigorous functional and structural neuroimaging studies that there is no consistent evidence to support the generalized version of the under-connectivity theory (Just *et al.*, 2004) or the local over- and distal under-connectivity hypothesis (Belmonte *et al.*, 2004) of brain organization in autism. In other words, distance and strength of connectivity as individual factors or as interacting factors do not consistently explain or predict the patterns of atypical neural connectivity in individuals with autism. In fact, there is strong contrary evidence. The data from rsfMRI studies are beginning to converge on findings of targeted under-connectivity among particular cortical regions in combination with subcortico-cortical *over-connectivity* (which does not qualify as a local connection according to Belmonte and colleagues). The task-based connectivity literature does not yield any consistent findings within or between domains, aside from revealing that the temporal lobe may be particularly vulnerable in individuals with autism. Finally, the structural

connectivity data are fairly disjointed from the functional data and, therefore, do not bolster or inform the functional connectivity data with regard to these original hypotheses. There is no consistent evidence of *local* over-connectivity in any measure of functional or structural connectivity.

As a result, we argue that the original hypotheses, particularly in their current form, are not supported by empirical evidence and, therefore, should no longer be viewed as general principles of brain organization in autism. If researchers continue to investigate these factors, we recommend that it will be crucial to define the distance and strength of connections more operationally. For example, long-range connections could be defined based on anatomical connections and/or functionally defined regions and short-range connections could be defined by microstructural properties of cell assemblies, and would probably need to be measured with higher resolution technology. Similarly, the strength of functional connectivity could be measured not only in the strength of a single connection (i.e. magnitude of correlation), but also in the number of functional connections (e.g. presence of connections as determined in SEM) or whether a long-range structural connection exists to enable more direct functional communication between distal regions.

In the face of the conclusion that distance and strength of connectivity do not consistently explain the patterns of atypical neural connectivity in individuals with autism, we suggest alternative conceptual approaches and make several methodological recommendations that will help researchers develop new hypotheses about the nature and mechanisms of potentially aberrant functional and structural connectivity in autism.

Developmental lens

Although Belmonte's original hypothesis was conceptualized as a developmental framework, it does not consider the mechanisms of typical brain development that may be subject to perturbation in autism populations. This represents a substantial limitation of this framework given that the functional, structural, and intrinsic connectivity are all dynamically changing across the lifespan in TD individuals and, as such, should be considered when making hypotheses about how trajectories in autism may be altered (i.e. different from the typical trajectory). Thus, we propose that researchers examining connectivity in autism populations should look to the normative development literature as benchmarks for thinking about brain development in autism. Here, we will briefly review what studies of typical brain development have revealed,

and how this literature may or may not allow us to reflect on Belmonte's original hypothesis.

Emerging findings from longitudinal studies in typical development

In terms of structure (i.e. DTI and tractography), there is beginning to be convergence across longitudinal studies of typical development (for review, see Khundrakpam, Lewis, Zhao, Chouinard-Decorte & Evans, 2016). Specifically, there seems to be protracted development of long-range white matter tracts that extends into young adulthood (Baker, Lubman, Yücel, Allen, Whittle *et al.*, 2015; Giedd, Blumenthal, Jeffries, Castellanos, Liu *et al.*, 1999; Lebel & Beaulieu, 2011; Krogsrud, Fjell, Tamnes, Grydeland, Mork *et al.*, 2016; Simmonds, Hallquist, Asato & Luna, 2014; Walker, Chang, Nayak, Irfanoglu, Botteron *et al.*, 2016). At the regional (more local) level, the thalamus, medial temporal lobes, the cerebellum, and portions of the occipital lobe mature extensively from late childhood into adolescence (Simmonds *et al.*, 2014). In this way, both local (i.e. regionally specific) and long-range structural connections are strengthening across the first two decades of life; there does not appear to be a temporal precedence for one over the other. Recall, Belmonte *et al.* proposed that there is a temporal priority of aberrant development of local connections that lead to disrupted long-range connections in autism. However, the TD literature suggests that the trajectories of these local and distal tracts are occurring simultaneously, indicating that Belmonte's hypothesis may not make sense developmentally, or even biologically.

Using a developmental approach to study neural connectivity in autism

There are several reasons why it is essential that researchers take more of a developmental approach in the acquisition and interpretation of connectivity findings in future research (see next section for methodological reasons). First, childhood and adolescence represent different periods of brain development in the processes of myelination, synaptogenesis and synaptic pruning (Gogtay, Giedd, Lusk, Hayashi, Greenstein *et al.*, 2004; Huttenlocher, 2002; Lebel & Beaulieu, 2011; Lossi & Merighi, 2003; Petanjek, Judaš, Šimić, Rašin, Uylings *et al.*, 2011), which all potentially impact the analysis of functional and structural connectivity data. Importantly, there are developmental hypotheses in the literature that these processes might unfold at different rates among individuals with autism (e.g. Courchesne, Pierce, Schumann, Redcay, Buckwalter *et al.*, 2007; Wolff, Gu, Gerig, Elison, Styner *et al.*, 2012). Therefore, we implore

researchers to be particularly mindful that comparing children and adolescents, even among TD children, can reveal dramatic nonlinear differences.

Second, the prominent symptoms of autism and their manifestation change across development. For example, while repetitive sensorimotor behaviors are fairly consistent across childhood, insistence on sameness increases over this same period (Richler, Huerta, Bishop & Lord, 2010). These changing behaviors and manifestations of behavioral symptoms are likely to be reflected in changing neural organization. This could also help explain why there are such huge discrepancies in the literature regarding the profile of both resting-state and task-based functional neural networks and whether they are related to symptom profiles. Third, there may be particular developmental periods that present differential vulnerabilities (or strengths) for individuals with autism both compared to themselves at other developmental periods (e.g. late childhood) and compared to TD individuals in the same developmental period. For example, we have recently written about the likelihood that adolescence is a developmental period of vulnerability in autism (Picci & Scherf, 2015), which is supported by both behavioral and neuroimaging findings (e.g. Scherf, Behrmann, Kimchi & Luna, 2009; Scherf, Luna, Minshew & Behrmann, 2010; Scherf *et al.*, 2015; Whyte *et al.*, 2016). Taking a developmental perspective with this in mind could lead to hypotheses about how neural networks are changing in adolescence. That is, neural network development may be differentially related to social symptoms in adolescence compared to childhood (when they might be more related to repetitive behavior). Taking this perspective may help in stratifying individuals in a developmentally sensitive way, instead of thinking about properties of neural networks as trait-like and fixed throughout development (e.g. always under-connected).

Many prior studies seem to collapse participants across age into a single group. We argue that it is highly likely that neural circuits are undergoing impressive, potentially nonlinear, changes across the developmental periods of childhood, adolescence, and even emerging adulthood. The implication is that the *developmental trajectories* for changes in neural organization could vary enormously for individuals with autism and that collapsing across broad age ranges prohibits us from being able to capture this critical finding. Uddin and colleagues (2013) also underscore the importance of considering developmentally sensitive time frames when evaluating models of connectivity in autism. Consistent with this notion, recent empirical findings indicate that there are important age-related differences in the profile of resting-state functional connectivity differences between

TD individuals and those with autism in childhood, adolescence, and adulthood (Alaerts, Nayar, Kelly, Raithel, Milham *et al.*, 2015; Long, Duan, Mantini & Chen, 2016; Nomi & Uddin, 2015) that are not captured simply as a function of distance. For example, Long and colleagues (2016) report functional under-connectivity at both local and distal distances in children, adolescents, and adults with autism (Long *et al.*, 2016). This study was able to establish a diagnosis \times age \times distance interaction such that children with autism exhibited lower short-range connectivity compared to adolescents and adults with autism, suggesting that there are important developmental changes occurring at the neural level in individuals with autism.

In the same vein, it may be important for future work to examine *change* across shorter time scales. That is, we suggest that researchers begin to think about network organization at a more gestalt level and in terms of dynamic properties. To date, much of the literature evaluates connectivity between pairs of regions and often discusses the profile of connections that are observed as if they represent fixed properties of the networks. While this may be a more fair characterization of structural networks (although see Fields, Woo & Bassler, 2015), functional neural networks have the potential to be much more dynamic (Liu & Duyn, 2013). We encourage researchers to conceptualize functional neural networks in terms of self-organizing systems that exhibit relatively short-lived meta-stable states (Hutchinson & Morton, 2015) in which small changes to the strength of the connections can lead to important computational changes that are relevant for behavior. This will require the creation of new multivariate approaches to capture patterns of connections across large numbers of nodes in networks (e.g. Coben, Mohammad-Rezazadeh & Canon, 2014). This conceptualization is reminiscent of a dynamic systems or a connectionist approach (i.e. concepts self-organization and emergent properties of systems), which may yield a more accurate representation of emergent patterns of activity and organization in brain functioning in autism. That is, being able to quantify state changes via attractor and repellant states could offer a more explanatory framework for brain and behavior relationships in autism (and in typical brain development as well). In addition, this approach would be more amenable to understanding dynamic changes in connectivity that emerge across development, and/or as a result of within-group individual differences. In this way, using a more dynamic systems perspective on the organization of neural networks could lead to the development of methodological and analytic techniques that more adequately capture the emergence and fluctuation of brain states (e.g. Davison, Schlesinger, Bassett,

Lynall, Miller *et al.*, 2015), which might be a more clear reflection of what is atypical in autism.

In so doing, researchers interested in the developmental course of neural connectivity patterns in autism can begin to gain a more 'bird's eye view' perspective of network-level interactions. For example, resting-state studies are employing graph theory metrics from network neuroscience to capture the network architecture at both the global and node levels. To our knowledge, only three studies to date have used these metrics to evaluate group differences in network architecture in autism (You *et al.*, 2013; Ray *et al.*, 2014; Rudie *et al.*, 2013). We suggest that this is likely to be a fruitful approach for assessing potential network differences across development in the future.

Since the publication of Belmonte's paper, only one other paper has underscored the importance of considering development (Uddin *et al.*, 2013). In Uddin and colleagues' (2013) paper, they highlight the importance of considering individual differences and age for understanding how profiles of functional connectivity might differ between typically developing individuals and those with autism, particularly in childhood versus adulthood. We suggest that age is an important factor to consider because it is a widespread predictor of brain development in typically developing individuals (see Baker *et al.*, 2015; Giedd *et al.*, 1999; Lebel & Beaulieu, 2011; Krogsrud *et al.*, 2016; Simmonds *et al.*, 2014; Walker *et al.*, 2016). However, it is also a low fidelity measure that does not provide information about specific mechanisms that shape brain development. We suggest that in order to understand mechanistic factors that influence atypical brain development in autism, researchers must begin to consider a wide range of mechanistic factors that are likely to impact brain development (e.g. SES, biological sex, pubertal development, critical experiences). In other words, we suggest that to fully capture the extent to which developmental trajectories of TD individuals and individuals with autism differ, we must go beyond *age* to evaluate and identify specific mechanistic factors of brain development.

Future recommendations

There are several methodological considerations we believe must be taken into account in future studies of connectivity in autism. First, given the clear impact of methodological variables on connectivity measures such as transient motion (Power *et al.*, 2012; van Dijk *et al.*, 2012), physiological artifacts (e.g. Birn, Murphy & Bandettini, 2008; Gotts *et al.*, 2012), hardware artifacts (e.g. Jo, Saad, Simmons, Milbury & Cox, 2010), as well

as preprocessing steps (e.g. Gotts *et al.*, 2013; Hahamy, Calhoun, Pearlson, Harel, Stern *et al.*, 2014; Nair *et al.*, 2014; Saad, Reynolds, Jo, Gotts, Chen *et al.*, 2013), it is critical for researchers to assess the impact of such artifacts on group comparisons and other analyses to the extent possible. Many researchers have begun to use multiple strategies to address these issues, including matching groups on measures such as motion and including the nuisance measures as covariates in analyses (e.g. see Power *et al.*, 2015; Saad *et al.*, 2013, for further discussion). Given the unresolved status of the best approaches for de-noising both functional and structural data, we also recommend that researchers examine their results against a variety of nuisance measures, including average Framewise Displacement (e.g. Power *et al.*, 2015), the global level of correlation (e.g. GCOR; Saad *et al.*, 2013), as well as average and local signal amplitude (e.g. Jones *et al.*, 2010; Gotts *et al.*, 2012) and conduct tests with matched groups on such factors whenever possible. Although functional connectivity studies, and rsfMRI studies in particular, have seen appreciable improvement in sample sizes and replication attempts with the advent of ABIDE, task-based functional connectivity and structural connectivity studies lag behind and often remain under powered. Therefore, we recommend that additional effort be focused on replicating initial functional task-based connectivity findings using the same tasks and methods with larger samples, perhaps by using data sharing initiatives. Given the recent concerns with widespread methods of cluster-size correction by Gaussian random field Monte Carlo simulations in popular neuroimaging software tools (such as SPM, FSL, and AFNI; Eklund, Nichols & Knutsson, 2015), we also recommend that all cluster-corrected results be checked by random permutation methods and emphasize that corrections adjust not only for whole-brain, voxelwise testing but also the number of independent seed tests performed.

In addition, given that autism is an extremely heterogeneous disorder, we contend that this should be of principal concern in the design, preprocessing, and analysis of connectivity studies. In other words, instead of thinking about the heterogeneity as noise that complicates analyses, it may provide critical information about mechanisms underlying potentially atypical patterns of connectivity. For example, several studies have reported that individual differences in symptom severity are related to variations in connectivity patterns (Abrams *et al.*, 2013; Gotts *et al.*, 2012; Hahamy *et al.*, 2015; Keown *et al.*, 2013; Redcay, Moran, Mavros, Tager-Flusberg, Gabrieli *et al.*, 2013; Supekar, Uddin, Khouzam, Phillips, Gaillard *et al.*, 2013; Weng, Wiggins, Peltier, Carrasco, Risi *et al.*, 2010). Understanding how neural connectivity

patterns relate to individual differences in symptom severity or variations in phenotypic behavior may have the potential to identify biomarkers specific to autism disorders. In the same vein, although there are many domains in which people with autism struggle, we suggest that future task-based connectivity studies target behavioral domains in which there are a broad range of individual differences in the extent to which people with autism are impacted (i.e. those that elicit more heterogeneous performance). For example, people with autism may show fairly consistent performance in their ability to discriminate a face from an object. As a result, observing task-based functional connectivity patterns while they do so may not be very informative about the nature of atypical neural organization for autism as a whole or in terms of understanding what about atypical neural network organization might be related to more severe social symptoms in autism. In contrast, there is likely to be much more variability in the extent to which people with autism can discriminate subtle emotional expressions from a neutral expression. Therefore, characterizing the functional network organization during this kind of task may provide critical information about how systematic variations in atypical network organization are related to atypical social behavior in autism.

As previously mentioned, there are several studies that have addressed individual differences within autism by attempting to relate neural connectivity measures to behavior (e.g. on the basis of sex; Ypma, Moseley, Holt, Rughooputh, Floris *et al.*, 2016) and symptom severity. Taking this approach can be especially fruitful in considering the developmental course of potentially aberrant neural connectivity in autism. Several recent MEG studies report that connectivity in children and adolescents with autism predicts symptom severity on either the ADOS or SRS (Cornew *et al.*, 2012; Edgar *et al.*, 2015; Ghanbari *et al.*, 2015). Another study using rsfMRI evaluated the extent to which social impairments relate to profiles of connectivity in regions implicated in social functioning among adolescents with autism and TD controls (Gotts *et al.*, 2012). They reported that the extent of *social* symptom severity in the participants with autism was predicted by underconnectivity among limbic, frontal, and temporal regions, all of which have previously been associated with aspects of social behavior. These are just two examples in which careful consideration of individual differences has led to more nuanced findings about patterns of atypical neural connectivity that are not simply characterized as a function of distance, and therefore are not adequately explained by the Belmonte and Just hypotheses.

One major caveat of the current literature is its exclusion of low-functioning individuals with autism,

which may contribute immensely to our understanding of individual differences in connectivity in autism. Researchers have largely focused their efforts on ensuring that participants with autism and their TD comparisons are matched on measures of IQ (particularly non-verbal IQ). While this is important for controlling a potentially confounding variable, it is unfortunate in its lack of generalizability to the broader autism population. That is, only approximately 30% of individuals with autism score within the normal range of FSIQ (Yeargin-Allsopp, Rice, Karapurkar, Doernberg, Boyle *et al.*, 2003), which suggests that most connectivity studies including participants with autism are likely only characterizing about one-third of this population. There may be limitations to being able to conduct imaging experiments successfully with the broader autism population, particularly in task-based experiments. However, with the advent of resting-state methodologies that do not require participants to perform a task, there is opportunity to gain better understanding of the individual differences within autism as a function of variables such as IQ as well as other comorbidities. This should be a priority of future work, given that comorbidities are extremely common in individuals with autism (Hurtig, Kuusikko, Mattila, Haapsamo, Ebeling *et al.*, 2009; Leyfer, Folstein, Bacalman, Davis, Dinh *et al.*, 2006; Mayes, Calhoun, Murray, Ahuja & Smith, 2011). Therefore, future experiments designed to carefully consider individual differences that stratify individuals within the larger autism population will better serve to uncover the underlying mechanisms of autism, and not just a subset of this population.

On the other hand, the heterogeneity of autism can lead to major issues within a single study. For example, if the brains of people with autism are organized in more idiosyncratic ways, particularly in terms of the organization of the white matter fiber tracts, this will make the strategies for co-registration into a common reference space for group-level analyses potentially difficult, as is needed for many kinds of whole-brain analyses (e.g. TBSS; Smith, Johansen-Berg, Jenkinson, Rueckert, Nichols *et al.*, 2007). Also, the symptoms of autism manifest differently across age and people with autism exhibit developmental change across many domains (see Picci & Scherf, 2015). As a result, including participants across a large age range (e.g. 8–35 years), as most of the existing studies do, likely introduces developmental heterogeneity. In fact, Uddin and colleagues recently proposed that discrepancies in findings from existing resting state studies may be largely due to the age range of the participants (Uddin *et al.*, 2013). In support of this idea, there is a large body of work reporting that functional connectivity, particularly resting-state connectivity, changes with age in childhood and adolescence

among TD individuals (e.g. for review see Ernst, Torrisi, Balderston, Grillon & Hale, 2015) and those with autism (e.g. Alaerts *et al.*, 2015; Dajani & Uddin, 2015; Greene, Laumann, Dubis, Ihnen, Neta *et al.*, 2014; Nomi & Uddin, 2015). As a result, we recommend that future studies avoid introducing unnecessary levels of heterogeneity into their data, especially by collapsing vastly different age ranges into a single group for group-level analyses. Critically, averaging across a wide range of ages (e.g. averaging children and adolescents together) could actually wash out important developmental differences and effects that are a product of developmental transitions in autism (and TD) development.

Conclusions

For nearly a decade, the neural connectivity theories of autism have been dominated by the under-connectivity theory (Just *et al.*, 2004) and Belmonte and colleagues' (2004) local-over distal-under-connectivity hypothesis. To put this into perspective, since the publication of these articles, they have been cited 1197 times and 792 times, respectively (these numbers increase weekly). These citation numbers demonstrate the pervasive impact of these claims. Since their publication, the field has expanded immensely, and undergone a methodological revolution. As a result, the most rigorous findings are now revealing how deeply complex the story is regarding atypical neural network organization in autism. From rsfMRI studies, there is an emerging consensus of cortico-cortical under-connectivity specifically involving the temporal lobes combined with subcortical-cortical over-connectivity. In contrast, there is little or no consensus regarding local connectivity or findings from task-based connectivity studies. The structural connectivity data also suggest that the temporal lobe tracts are vulnerable. We recommend alternative methods and ways of approaching the study of neural connectivity in autism with careful attention to individual differences and developmental mechanisms that can ultimately help to move the field forward.

Author contributions

GP, SG and KSS conceptualized and wrote the article together.

Acknowledgements

This work was supported by Pennsylvania Department of Health SAP grant 4100047862 (to KSS – Co-PI), the

Social Science Research Institute and the Department of Psychology at the Pennsylvania State University as well as a Graduate Research Fellowship from the National Science Foundation to GP (# DGE1255832). Any opinions, findings, and conclusions or recommendations expressed in this material are those of the authors and do not necessarily reflect the views of the National Science Foundation. This work was also supported by the National Institute of Mental Health, NIH, Division of Intramural Research (to SG).

References

- Abrams, D.A., Lynch, C.J., Cheng, K.M., Phillips, J., Supekar, K. *et al.* (2013). Underconnectivity between voice-selective cortex and reward circuitry in children with autism. *Proceedings of the National Academy of Sciences, USA*, **110** (29), 12060–12065.
- Adolphs, R. (2009). The social brain: neural basis of social knowledge. *Annual Review of Psychology*, **60**, 693–716.
- Alaerts, K., Di Martino, A., Swinnen, S., & Wenderoth, N. (2013). Underconnectivity of STS predicts socio-cognitive deficits in autism. *Biological Psychiatry*, **73** (9), 87S–87S.
- Alaerts, K., Nayar, K., Kelly, C., Raithel, J., Milham, M.P. *et al.* (2015). Age-related changes in intrinsic function of the superior temporal sulcus in autism spectrum disorders. *Social Cognitive and Affective Neuroscience*, **10** (10), 1413–1423.
- Alaerts, K., Woolley, D.G., Steyaert, J., Di Martino, A., Swinnen, S.P. *et al.* (2014). Underconnectivity of the superior temporal sulcus predicts emotion recognition deficits in autism. *Social Cognitive and Affective Neuroscience*, **9** (10), 1589–1600.
- Ambrosino, S., Bos, D.J., van Raalten, T.R., Kobussen, N.A., van Belle, J. *et al.* (2014). Functional connectivity during cognitive control in children with autism spectrum disorder: an independent component analysis. *Journal of Neural Transmission*, **121** (9), 1145–1155.
- Anderson, J.S., Nielsen, J.A., Froehlich, A.L., DuBray, M.B., Druzgal, T.J. *et al.* (2011). Functional connectivity magnetic resonance imaging classification of autism. *Brain*, **134** (12), 3742–3754.
- Anticevic, A., Cole, M.W., Repovs, G., Savic, A., Driesen, N.R. *et al.* (2013). Connectivity, pharmacology, and computation: toward a mechanistic understanding of neural system dysfunction in schizophrenia. *Frontiers in Psychiatry*, **4**, 169.
- Baker, S.T., Lubman, D.I., Yücel, M., Allen, N.B., Whittle, S. *et al.* (2015). Developmental changes in brain network hub connectivity in late adolescence. *Journal of Neuroscience*, **35** (24), 9078–9087.
- Barbeau, E.B., Lewis, J.D., Doyon, J., Benali, H., Zeffiro, T.A. *et al.* (2015). A greater involvement of posterior brain areas in interhemispheric transfer in autism: fMRI, DWI and behavioral evidences. *NeuroImage: Clinical*, **8**, 267–280.
- Belmonte, M.K., Allen, G., Beckel-Mitchener, A., Boulanger, L.M., Carper, R.A. *et al.* (2004). Autism and abnormal development of brain connectivity. *Journal of Neuroscience*, **24** (42), 9228–9231.
- Birn, R.M., Murphy, K., & Bandettini, P.A. (2008). The effect of respiration variations on independent component analysis results of resting state functional connectivity. *Human Brain Mapping*, **29**, 740–750.
- Biswal, B., Zerrin Yetkin, F., Haughton, V.M., & Hyde, J.S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magnetic Resonance in Medicine*, **34** (4), 537–541.
- Bos, D.J., van Raalten, T.R., Oranje, B., Smits, A.R., Kobussen, N.A. *et al.* (2014). Developmental differences in higher-order resting-state networks in autism spectrum disorder. *NeuroImage: Clinical*, **4**, 820–827.
- Cerliani, L., Mennes, M., Thomas, R.M., Di Martino, A., Thioux, M. *et al.* (2015). Increased functional connectivity between subcortical and cortical resting-state networks in autism spectrum disorder. *JAMA Psychiatry*, **72** (8), 767–777.
- Cheng, W., Rolls, E.T., Zhang, J., & Feng, J. (2015). Autism: reduced connectivity between cortical areas involved in face expression, theory of mind, and the sense of self. *Brain*, **138** (5), 1382–1393.
- Chien, H.-Y., Lin, H.-Y., Lai, M.-C., Gau, S.S.-F., & Tseng, W.-Y.I. (2015). Hyperconnectivity of the right posterior temporo-parietal junction predicts social difficulties in boys with autism spectrum disorder. *Autism Research*, **8** (4), 427–441. doi:10.1002/aur.1457
- Coben, R., Clarke, A.R., Hudspeth, W., & Barry, R.J. (2008). EEG power and coherence in autistic spectrum disorder. *Clinical Neurophysiology*, **119** (5), 1002–1009.
- Coben, R., Mohammad-Rezazadeh, I., & Cannon, R.L. (2014). Using quantitative and analytic EEG methods in the understanding of connectivity in autism spectrum disorders: a theory of mixed over- and under-connectivity. *Frontiers in Human Neuroscience*, **8**, 45.
- Cornew, L., Roberts, T.P., Blaskey, L., & Edgar, J.C. (2012). Resting-state oscillatory activity in autism spectrum disorders. *Journal of Autism and Developmental Disorders*, **42** (9), 1884–1894.
- Courchesne, E., Pierce, K., Schumann, C.M., Redcay, E., Buckwalter, J.A. *et al.* (2007). Mapping early brain development in autism. *Neuron*, **56** (2), 399–413.
- Dajani, D.R., & Uddin, L.Q. (2015). Local brain connectivity across development in autism spectrum disorder: a cross-sectional investigation. *Autism Research*, **9** (1), 43–54.
- Davison, E.N., Schlesinger, K.J., Bassett, D.S., Lynall, M.E., Miller, M.B. *et al.* (2015). Brain network adaptability across task states. *PLoS Computational Biology*, **11** (1), e1004029.
- Delmonte, S., Gallagher, L., O’Hanlon, E., McGrath, J., & Balsters, J.H. (2013). Functional and structural connectivity of frontostriatal circuitry in autism spectrum disorder. *Frontiers in Human Neuroscience*, **7**, 430.
- Deshpande, G., Liberio, L.E., Sreenivasan, K.R., Deshpande, H.D., & Kana, R.K. (2013). Identification of neural

- connectivity signatures of autism using machine learning. *Frontiers in Human Neuroscience*, **7**, 670.
- Di Martino, A., Kelly, C., Grzadzinski, R., Zuo, X.N., Mennes, M. *et al.* (2011). Aberrant striatal functional connectivity in children with autism. *Biological Psychiatry*, **69** (9), 847–856.
- Di Martino, A., Yan, C.G., Li, Q., Denio, E., Castellanos, F.X. *et al.* (2014). The autism brain imaging data exchange: towards a large-scale evaluation of the intrinsic brain architecture in autism. *Molecular Psychiatry*, **19** (6), 659–667.
- Dinstein, I., Heeger, D.J., Lorenzi, L., Minshew, N.J., Malach, R. *et al.* (2012). Unreliable evoked responses in autism. *Neuron*, **75**, 981–991.
- Domínguez, L.G., Velázquez, J.L.P., & Galán, R.F. (2013). A model of functional brain connectivity and background noise as a biomarker for cognitive phenotypes: application to autism. *PLoS ONE*, **8** (4), e61493.
- Ebisch, S.J., Gallese, V., Willems, R.M., Mantini, D., Groen, W.B. *et al.* (2011). Altered intrinsic functional connectivity of anterior and posterior insula regions in high-functioning participants with autism spectrum disorder. *Human Brain Mapping*, **32**, 1013–1028.
- Edgar, J.C., Heiken, K., Chen, Y.H., Herrington, J.D., Chow, V. *et al.* (2015). Resting-state alpha in autism spectrum disorder and alpha associations with thalamic volume. *Journal of Autism and Developmental Disorders*, **45** (3), 795–804.
- Eklund, A., Nichols, T., & Knutsson, H. (2015). Can parametric statistical methods be trusted for fMRI based group studies? *arXiv preprint arXiv:1511.01863*.
- Ernst, M., Torrisi, S., Balderston, N., Grillon, C., & Hale, E.A. (2015). fMRI functional connectivity applied to adolescent neurodevelopment. *Annual Review of Clinical Psychology*, **11**, 361–377.
- Fair, D.A., Bathula, D., Mills, K.L., Dias, T.G.C., Blythe, M.S. *et al.* (2010). Maturing thalamocortical functional connectivity across development. *Frontiers in Systems Neuroscience*, **4**, 10.
- Fields, R.D., Woo, D.H., & Basser, P.J. (2015). Glial regulation of the neuronal connectome through local and long-distant communication. *Neuron*, **86** (2), 374–386.
- Fishman, I., Datko, M., Cabrera, Y., Carper, R.A., & Müller, R.A. (2015). Reduced integration and differentiation of the imitation network in autism: a combined functional connectivity magnetic resonance imaging and diffusion-weighted imaging study. *Annals of Neurology*, **78** (6), 958–969.
- Fitzgerald, J., Johnson, K., Kehoe, E., Bokde, A.L., Garavan, H. *et al.* (2015). Disrupted functional connectivity in dorsal and ventral attention networks during attention orienting in autism spectrum disorders. *Autism Research*, **8** (2), 136–152.
- Fox, M.D., & Raichle, M.E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature Reviews Neuroscience*, **8** (9), 700–711.
- Frith, C.D., & Frith, U. (2007). Social cognition in humans. *Current Biology*, **17**, R724–R732.
- Ghanbari, Y., Bloy, L., Edgar, J.C., Blaskey, L., Verma, R. *et al.* (2015). Joint analysis of band-specific functional connectivity and signal complexity in autism. *Journal of Autism and Developmental Disorders*, **45** (2), 444–460.
- Ghuman, A.S., McDaniel, J.R., & Martin, A. (2011). A wavelet-based method for measuring the oscillatory dynamics of resting-state functional connectivity in MEG. *NeuroImage*, **56** (1), 69–77.
- Giedd, J.N., Blumenthal, J., Jeffries, N.O., Castellanos, F.X., Liu, H. *et al.* (1999). Brain development during childhood and adolescence: a longitudinal MRI study. *Nature Neuroscience*, **2** (10), 861–863.
- Gogtay, N., Giedd, J.N., Lusk, L., Hayashi, K.M., Greenstein, D. *et al.* (2004). Dynamic mapping of human cortical development during childhood through early adulthood. *Proceedings of the National Academy of Sciences, USA*, **101** (21), 8174–8179.
- Gotts, S.J., Saad, Z.S., Jo, H.J., Wallace, G.L., Cox, R.W. *et al.* (2013). The perils of global signal regression for group comparisons: a case study of autism spectrum disorders. *Frontiers in Human Neuroscience*, **7**, 356.
- Gotts, S.J., Simmons, W.K., Milbury, L.A., Wallace, G.L., & Cox, R.W. *et al.* (2012). Fractionation of social brain circuits in autism spectrum disorders. *Brain*, **135** (Part 9), 2711–2725.
- Greene, D.J., Laumann, T.O., Dubis, J.W., Ihnen, S.K., Neta, M. *et al.* (2014). Developmental changes in the organization of functional connections between the basal ganglia and cerebral cortex. *Journal of Neuroscience*, **34**, 5842–5854.
- Hahamy, A., Behrmann, M., & Malach, R. (2015). The idiosyncratic brain: distortion of spontaneous connectivity patterns in autism spectrum disorder. *Nature Neuroscience*, **18**, 302–309.
- Hahamy, A., Calhoun, V., Pearlson, G., Harel, M., Stern, N. *et al.* (2014). Save the global: global signal regression as a tool for studying clinical populations with functional magnetic resonance imaging. *Brain Connectivity*, **4**, 395–403.
- Hanaie, R., Mohri, I., Kagitani-Shimono, K., Tachibana, M., Matsuzaki, J. *et al.* (2014). Abnormal corpus callosum connectivity, socio-communicative deficits, and motor deficits in children with autism spectrum disorder: a diffusion tensor imaging study. *Journal of Autism and Developmental Disorders*, **44** (9), 2209–2220.
- Hebb, D.O. (1949). *The organization of behavior: A neuropsychological approach*. New York: John Wiley & Sons.
- Hurtig, T., Kuusikko, S., Mattila, M.L., Haapsamo, H., Ebeling, H. *et al.* (2009). Multi-informant reports of psychiatric symptoms among high-functioning adolescents with Asperger syndrome or autism. *Autism*, **13** (6), 583–598.
- Hutchison, R.M., & Morton, J.B. (2015). Tracking the brain's functional coupling dynamics over development. *Journal of Neuroscience*, **35** (17), 6849–6859.
- Huttenlocher, P.R. (2002). Morphometric study of human cerebral cortex development. In M.H. Johnson, Y. Munakata & R.O. Gilmore (Eds.), *Brain development and cognition: A reader* (2nd edn., pp. 117–128). Oxford: Blackwell.
- Itahashi, T., Yamada, T., Watanabe, H., Nakamura, M., Jimbo, D. *et al.* (2014). Altered network topologies and hub organization in adults with autism: a resting-state fMRI study. *PLoS ONE*, **9** (4), e94115.

- Jo, H.J., Saad, Z.S., Simmons, W.K., Milbury, L.A., & Cox, R.W. (2010). Mapping sources of correlation in resting state fMRI, with artifact detection and removal. *NeuroImage*, **52**, 571–582.
- Jones, T.B., Bandettini, P.A., Kenworthy, L., Case, L.K., Milleville, S.C. *et al.* (2010). Sources of group differences in functional connectivity: an investigation applied to autism spectrum disorder. *NeuroImage*, **49** (1), 401–414.
- Joseph, R.M., Keehn, B., Connolly, C., Wolfe, J.M., & Horowitz, T.S. (2009). Why is visual search superior in autism spectrum disorder? *Developmental Science*, **12** (6), 1083–1096.
- Just, M.A., Cherkassky, V.L., Keller, T.A., & Minshew, N.J. (2004). Cortical activation and synchronization during sentence comprehension in high-functioning autism: evidence of underconnectivity. *Brain*, **127** (8), 1811–1821.
- Kaldy, Z., Kraper, C., Carter, A.S., & Blaser, E. (2011). Toddlers with autism spectrum disorder are more successful at visual search than typically developing toddlers. *Developmental Science*, **14** (5), 980–988.
- Kana, R.K., Uddin, L.Q., Kenet, T., Chugani, D., & Müller, R.A. (2014). Brain connectivity in autism. *Frontiers in Human Neuroscience*, **8**, 349.
- Keehn, B., Shih, P., Brenner, L.A., Townsend, J., & Müller, R.A. (2013). Functional connectivity for an ‘Island of sparing’ in autism spectrum disorder: an fMRI study of visual search. *Human Brain Mapping*, **34** (10), 2524–2537.
- Keown, C.L., Shih, P., Nair, A., Peterson, N., Mulvey, M.E. *et al.* (2013). Local functional overconnectivity in posterior brain regions is associated with symptom severity in autism spectrum disorders. *Cell Reports*, **5** (3), 567–572.
- Khan, S., Gramfort, A., Shetty, N.R., Kitzbichler, M.G., Ganesan, S. *et al.* (2013). Local and long-range functional connectivity is reduced in concert in autism spectrum disorders. *Proceedings of the National Academy of Sciences, USA*, **110** (8), 3107–3112.
- Khundrakpam, B.S., Lewis, J.D., Zhao, L., Chouinard-Decorte, F., & Evans, A.C. (2016). Brain connectivity in normally developing children and adolescents. *NeuroImage*, **134**, 192–203.
- Kikuchi, M., Yoshimura, Y., Mutou, K., & Minabe, Y. (2015). Magnetoencephalography in the study of children with autism spectrum disorder. *Psychiatry and Clinical Neurosciences*, **70** (2), 74–88.
- Kikuchi, M., Yoshimura, Y., Shitamichi, K., Ueno, S., Hiro-sawa, T. *et al.* (2013). A custom magnetoencephalography device reveals brain connectivity and high reading/decoding ability in children with autism. *Scientific Reports*, **3**, 1139.
- Kirkovski, M., Enticott, P.G., Maller, J.J., Rossell, S.L., & Fitzgerald, P.B. (2015). Diffusion tensor imaging reveals no white matter impairments among adults with autism spectrum disorder. *Psychiatry Research: Neuroimaging*, **233** (1), 64–72.
- Kitzbichler, M.G., Khan, S., Ganesan, S., Vangel, M.G., Herbert, M.R. *et al.* (2014). Altered development and multifaceted band-specific abnormalities of resting state networks in autism. *Biological Psychiatry*, **77** (9), 794–804.
- Koldewyn, K., Yendiki, A., Weigelt, S., Gweon, H., Julian, J. *et al.* (2014). Differences in the right inferior longitudinal fasciculus but no general disruption of white matter tracts in children with autism spectrum disorder. *Proceedings of the National Academy of Sciences, USA*, **111** (5), 1981–1986.
- Krogsrud, S.K., Fjell, A.M., Tamnes, C.K., Grydeland, H., Mork, L. *et al.* (2016). Changes in white matter microstructure in the developing brain: a longitudinal diffusion tensor imaging study of children from 4 to 11 years of age. *NeuroImage*, **124**, 473–486.
- Lebel, C., & Beaulieu, C. (2011). Longitudinal development of human brain wiring continues from childhood into adulthood. *Journal of Neuroscience*, **31** (30), 10937–10947.
- Lee, J.E., Bigler, E.D., Alexander, A.L., Lazar, M., DuBray, M.B. *et al.* (2007). Diffusion tensor imaging of white matter in the superior temporal gyrus and temporal stem in autism. *Neuroscience Letters*, **424** (2), 127–132.
- Leyfer, O.T., Folstein, S.E., Bacalman, S., Davis, N.O., Dinh, E. *et al.* (2006). Comorbid psychiatric disorders in children with autism: interview development and rates of disorders. *Journal of Autism and Developmental Disorders*, **36** (7), 849–861.
- Libero, L.E., Stevens, C.E., & Kana, R.K. (2014). Attribution of emotions to body postures: an independent component analysis study of functional connectivity in autism. *Human Brain Mapping*, **35** (10), 5204–5218.
- Liu, X., & Duyn, J.H. (2013). Time-varying functional network information extracted from brief instances of spontaneous brain activity. *Proceedings of the National Academy of Sciences, USA*, **110** (11), 4392–4397.
- Lombardo, M.V., Chakrabarti, B., Bullmore, E.T., Sadek, S.A., Pasco, G. *et al.* (2010). Atypical neural self-representation in autism. *Brain*, **133**, 611–624.
- Long, Z., Duan, X., Mantini, D., & Chen, H. (2016). Alteration of functional connectivity in autism spectrum disorder: Effect of age and anatomical distance. *Scientific Reports*, **6**, 26527.
- Lossi, L., & Merighi, A. (2003). In vivo cellular and molecular mechanisms of neuronal apoptosis in the mammalian CNS. *Progress in Neurobiology*, **69** (5), 287–312.
- Lynch, C.J., Uddin, L.Q., Supekar, K., Khouzam, A., Phillips, J. *et al.* (2013). Default mode network in childhood autism: posteromedial cortex heterogeneity and relationship with social deficits. *Biological Psychiatry*, **74** (3), 212–219.
- McGrath, J., Johnson, K., Ecker, C., O’Hanlon, E., Gill, M. *et al.* (2012). Atypical visuospatial processing in autism: insights from functional connectivity analysis. *Autism Research*, **5** (5), 314–330.
- McGrath, J., Johnson, K., O’Hanlon, E., Garavan, H., Gallagher, L. *et al.* (2013). White matter and visuospatial processing in autism: a constrained spherical deconvolution tractography study. *Autism Research*, **6** (5), 307–319.
- Mathewson, K.J., Jetha, M.K., Drmic, I.E., Bryson, S.E., Goldberg, J.O. *et al.* (2012). Regional EEG alpha power, coherence, and behavioral symptomatology in autism spectrum disorder. *Clinical Neurophysiology*, **123** (9), 1798–1809.

- Maximo, J.O., Cadena, E.J., & Kana, R.K. (2014). The implications of brain connectivity in the neuropsychology of autism. *Neuropsychology Review*, **24** (1), 16–31.
- Maximo, J.O., Keown, C.L., Nair, A., & Müller, R.A. (2013). Approaches to local connectivity in autism using resting state functional connectivity MRI. *Frontiers in Human Neuroscience*, **7**, 605.
- Mayes, S.D., Calhoun, S.L., Murray, M.J., Ahuja, M., & Smith, L.A. (2011). Anxiety, depression, and irritability in children with autism relative to other neuropsychiatric disorders and typical development. *Research in Autism Spectrum Disorders*, **5** (1), 474–485.
- Mitchell, J.P. (2009). Social psychology as a natural kind. *Trends in Cognitive Sciences*, **13**, 246–251.
- Mohammad-Rezazadeh, I., Frohlich, J., Loo, S.K., & Jeste, S.S. (2016). Brain connectivity in autism spectrum disorder. *Current Opinion in Neurology*, **29** (2), 137–147.
- Monk, C.S., Peltier, S.J., Wiggins, J.L., Weng, S.-J., Carrasco, M. *et al.* (2009). Abnormalities of intrinsic functional connectivity in autism spectrum disorders. *NeuroImage*, **47** (2), 764–772.
- Mueller, S., Keeser, D., Samson, A.C., Kirsch, V., Blautzik, J. *et al.* (2013). Convergent findings of altered functional and structural brain connectivity in individuals with high functioning autism: a multimodal MRI study. *PLoS ONE*, **8** (6), e67329.
- Müller, R.A., Shih, P., Keehn, B., Deyoe, J.R., Leyden, K.M. *et al.* (2011). Underconnected, but how? A survey of functional connectivity MRI studies in autism spectrum disorders. *Cerebral Cortex*, **21** (10), 2233–2243.
- Murias, M., Webb, S.J., Greenson, J., & Dawson, G. (2007). Resting state cortical connectivity reflected in EEG coherence in individuals with autism. *Biological Psychiatry*, **62** (3), 270–273.
- Murphy, E.R., Foss-Feig, J., Kenworthy, L., Gaillard, W.D., & Vaidya, C.J. (2012). Atypical functional connectivity of the amygdala in childhood autism spectrum disorders during spontaneous attention to eye-gaze. *Autism Research and Treatment*, doi:10.1155/2012/652408
- Nair, A., Keown, C.L., Datko, M., Shih, P., Keehn, B. *et al.* (2014). Impact of methodological variables on functional connectivity findings in autism spectrum disorders. *Human Brain Mapping*, **35** (8), 4035–4048.
- Nair, A., Treiber, J.M., Shukla, D.K., Shih, P., & Müller, R.A. (2013). Impaired thalamocortical connectivity in autism spectrum disorder: a study of functional and anatomical connectivity. *Brain*, **136** (6), 1942–1955.
- Nomi, J.S., & Uddin, L.Q. (2015). Developmental changes in large-scale network connectivity in autism. *NeuroImage: Clinical*, **7**, 732–741.
- Odriozola, P., Uddin, L.Q., Lynch, C.J., Kochalka, J., Chen, T. *et al.* (2015). Insula response and connectivity during social and non-social attention in children with autism. *Social Cognitive and Affective Neuroscience*, **11** (3), 433–444.
- Olson, I.R., Plotzker, A., & Ezzyat, Y. (2007). The enigmatic temporal pole: a review of findings on social and emotional processing. *Brain*, **130**, 1718–1731.
- Padmanabhan, A., Lynn, A., Foran, W., Luna, B., & O’Hearn, K. (2013). Age related changes in striatal resting state functional connectivity in autism. *Frontiers in Human Neuroscience*, **7**, 814.
- Petanjek, Z., Judaš, M., Šimić, G., Rašin, M.R., Uylings, H.B. *et al.* (2011). Extraordinary neoteny of synaptic spines in the human prefrontal cortex. *Proceedings of the National Academy of Sciences, USA*, **108** (32), 13281–13286.
- Picci, G., & Scherf, K.S. (2015). A two-hit model of autism: adolescence as the second hit. *Clinical Psychological Science*, **3** (3), 349–371.
- Power, J.D., Barnes, K.A., Snyder, A.Z., Schlaggar, B.L., & Petersen, S.E. (2012). Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *NeuroImage*, **59** (3), 2142–2154.
- Power, J.D., Barnes, K.A., Snyder, A.Z., Schlaggar, B.L., & Petersen, S.E. (2013). Steps toward optimizing motion artifact removal in functional connectivity MRI; a reply to Carp. *NeuroImage*, **76**, 439–441.
- Power, J.D., Schlaggar, B.L., & Petersen, S.E. (2014). Studying brain organization via spontaneous fMRI signal. *Neuron*, **84**, 681–696.
- Power, J.D., Schlaggar, B.L., & Petersen, S.E. (2015). Recent progress and outstanding issues in motion correction in resting state fMRI. *NeuroImage*, **105**, 536–551.
- Radulescu, E., Minati, L., Ganeshan, B., Harrison, N.A., Gray, M.A. *et al.* (2013). Abnormalities in fronto-striatal connectivity within language networks relate to differences in grey-matter heterogeneity in Asperger syndrome. *NeuroImage: Clinical*, **2**, 716–726.
- Rane, P., Cochran, D., Hodge, S.M., Haselgrove, C., Kennedy, D.N. *et al.* (2015). Connectivity in autism: a review of MRI connectivity studies. *Harvard Review of Psychiatry*, **23** (4), 223–244.
- Ray, S., Miller, M., Karalunas, S., Robertson, C., Grayson, D.S. *et al.* (2014). Structural and functional connectivity of the human brain in autism spectrum disorders and attention-deficit/hyperactivity disorder: a rich club-organization study. *Human Brain Mapping*, **35** (12), 6032–6048.
- Redcay, E., Moran, J.M., Mavros, P.L., Tager-Flusberg, H., Gabrieli, J.D. *et al.* (2013). Intrinsic functional network organization in high-functioning adolescents with autism spectrum disorder. *Frontiers in Human Neuroscience*, **7**, 573.
- Richler, J., Huerta, M., Bishop, S.L., & Lord, C. (2010). Developmental trajectories of restricted and repetitive behaviors and interests in children with autism spectrum disorders. *Development and Psychopathology*, **22** (01), 55–69.
- Rudie, J.D., Brown, J.A., Beck-Pancer, D., Hernandez, L.M., Dennis, E.L. *et al.* (2013). Altered functional and structural brain network organization in autism. *NeuroImage: Clinical*, **2**, 79–94.
- Saad, Z.S., Reynolds, R.C., Jo, H.J., Gotts, S.J., Chen, G. *et al.* (2013). Correcting brain-wide correlation differences in resting-state FMRI. *Brain Connectivity*, **3** (4), 339–352.
- Satterthwaite, T.D., & Baker, J.T. (2015). How can studies of resting-state functional connectivity help us understand

- psychosis as a disorder of brain development? *Current Opinion in Neurobiology*, **30**, 85–91.
- Satterthwaite, T.D., Wolf, D.H., Loughhead, J., Ruparel, K., Elliott, M.A. *et al.* (2012). Impact of in-scanner head motion on multiple measures of functional connectivity: relevance for studies of neurodevelopment in youth. *NeuroImage*, **60** (1), 623–632.
- Schaer, M., Ottet, M.C., Scariati, E., Dukes, D., Franchini, M. *et al.* (2013). Decreased frontal gyrification correlates with altered connectivity in children with autism. *Frontiers in Human Neuroscience*, **7**, 750.
- Scherf, K.S., Behrmann, M., Kimchi, R., & Luna, B. (2009). Emergence of global shape processing continues through adolescence. *Child Development*, **80** (1), 162–177.
- Scherf, K.S., Elbich, D., Minshew, N., & Behrmann, M. (2015). Individual differences in symptom severity and behavior predict neural activation during face processing in adolescents with autism. *NeuroImage: Clinical*, **7**, 53–67.
- Scherf, K.S., Luna, B., Minshew, N., & Behrmann, M. (2010). Location, location, location: alterations in the functional topography of face- but not object- or place-related cortex in adolescents with autism. *Frontiers in Human Neuroscience*, **4**, 26.
- Sharda, M., Midha, R., Malik, S., Mukerji, S., & Singh, N.C. (2015). Fronto-temporal connectivity is preserved during sung but not spoken word listening, across the autism spectrum. *Autism Research*, **8** (2), 174–186.
- Shukla, D.K., Keehn, B., & Müller, R.A. (2011). Tract-specific analyses of diffusion tensor imaging show widespread white matter compromise in autism spectrum disorder. *Journal of Child Psychology and Psychiatry*, **52** (3), 286–295.
- Simmonds, D.J., Hallquist, M.N., Asato, M., & Luna, B. (2014). Developmental stages and sex differences of white matter and behavioral development through adolescence: a longitudinal diffusion tensor imaging (DTI) study. *NeuroImage*, **92**, 356–368.
- Smith, S.M., Johansen-Berg, H., Jenkinson, M., Rueckert, D., Nichols, T.E. *et al.* (2007). Acquisition and voxelwise analysis of multi-subject diffusion data with tract-based spatial statistics. *Nature Protocols*, **2** (3), 499–503.
- Sporns, O., Chialvo, D.R., Kaiser, M., & Hilgetag, C.C. (2004). Organization, development and function of complex brain networks. *Trends in Cognitive Sciences*, **8** (9), 418–425.
- Stevens, M.C., Pearlson, G.D., & Calhoun, V.D. (2009). Changes in the interaction of resting-state neural networks from adolescence to adulthood. *Human Brain Mapping*, **30** (8), 2356–2366.
- Supekar, K., Uddin, L.Q., Khouzam, A., Phillips, J., Gaillard, W.D. *et al.* (2013). Brain hyperconnectivity in children with autism and its links to social deficits. *Cell Reports*, **5** (3), 738–747.
- Travers, B.G., Tromp, D.P., Adluru, N., Lange, N., Destiche, D. *et al.* (2015). Atypical development of white matter microstructure of the corpus callosum in males with autism: a longitudinal investigation. *Molecular Autism*, **6** (1), 1–15.
- Tyszka, J.M., Kennedy, D.P., Paul, L.K., & Adolphs, R. (2014). Largely typical patterns of resting-state functional connectivity in high-functioning adults with autism. *Cerebral Cortex*, **24** (7), 1894–1905.
- Uddin, L.Q. (2015). Idiosyncratic connectivity in autism: developmental and anatomical considerations. *Trends in Neurosciences*, **38** (5), 261–263.
- Uddin, L.Q., Supekar, K., & Menon, V. (2013). Reconceptualizing functional brain connectivity in autism from a developmental perspective. *Frontiers in Human Neuroscience*, **7**, 458.
- van den Heuvel, M.P., & Sporns, O. (2011). Rich-club organization of the human connectome. *Journal of Neuroscience*, **31** (44), 15775–15786.
- van Dijk, K.R., Sabuncu, M.R., & Buckner, R.L. (2012). The influence of head motion on intrinsic functional connectivity MRI. *NeuroImage*, **59** (1), 431–438.
- Vargas, C., Lopez-Jaramillo, C., & Vieta, E. (2013). A systematic literature review of resting-state network functional MRI in bipolar disorder. *Journal of Affective Disorders*, **150**, 727–735.
- Vasa, R.A., Mostofsky, S.H., & Ewen, J.B. (2016). The disrupted connectivity hypothesis of autism spectrum disorders: time for the next phase in research. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, **1** (3), 245–252.
- Vissers, M.E., Cohen, M.X., & Geurts, H.M. (2012). Brain connectivity and high functioning autism: a promising path of research that needs refined models, methodological convergence, and stronger behavioral links. *Neuroscience & Biobehavioral Reviews*, **36** (1), 604–625.
- von dem Hagen, E.A.H., Stoyanova, R.S., Baron-Cohen, S., & Calder, A.J. (2013). Reduced functional connectivity within and between ‘social’ resting state networks in autism spectrum conditions. *Social, Cognitive, and Affective Neuroscience*, **8**, 694–701.
- von Monakow, C. (1914). *Die Lokalisation im Grosshirn und Abbau der Funktion durch kortikale Herde* [Localization in the cortex and the reduction of cortical function]. Wiesbaden: Bergman.
- Walker, L., Chang, L.C., Nayak, A., Irfanoglu, M.O., Botteron, K.N. *et al.* (2016). The diffusion tensor imaging (DTI) component of the NIH MRI study of normal brain development (PedsDTI). *NeuroImage*, **124**, 1125–1130.
- Weisberg, J., Milleville, S.C., Kenworthy, L., Wallace, G.L., Gotts, S.J. *et al.* (2014). Social perception in autism spectrum disorders: impaired category selectivity for dynamic but not static images in ventral temporal cortex. *Cerebral Cortex*, **24** (1), 37–48.
- Weng, S.J., Carrasco, M., Swartz, J.R., Wiggins, J.L., Kurapati, N. *et al.* (2011). Neural activation to emotional faces in adolescents with autism spectrum disorders. *Journal of Child Psychology and Psychiatry*, **52** (3), 296–305.
- Weng, S.J., Wiggins, J.L., Peltier, S.J., Carrasco, M., Risi, S. *et al.* (2010). Alterations of resting state functional connectivity in the default network in adolescents with autism spectrum disorders. *Brain Research*, **1313**, 202–214.
- Wernicke, C. (1900). *Grundriss der Psychiatrie*. Leipzig: Verlag von Georg Thieme.

- Whyte, E.M., Behrmann, M., Minshew, N.J., Garcia, N.V., & Scherf, K.S. (2016). Animal, but not human, faces engage the distributed face network in adolescents with autism. *Developmental Science*, **19** (2), 306–317.
- Williams, D.L., Cherkassky, V.L., Mason, R.A., Keller, T.A., Minshew, N.J. *et al.* (2013). Brain function differences in language processing in children and adults with autism. *Autism Research*, **6** (4), 288–302.
- Wolff, J.J., Gu, H., Gerig, G., Elison, J.T., Styner, M. *et al.* (2012). Differences in white matter fiber tract development present from 6 to 24 months in infants with autism. *American Journal of Psychiatry*, **169** (6), 589–600.
- Ye, A.X., Leung, R.C., Schäfer, C.B., Taylor, M.J., & Doesburg, S.M. (2014). Atypical resting synchrony in autism spectrum disorder. *Human Brain Mapping*, **35** (12), 6049–6066.
- Yeargin-Allsopp, M., Rice, C., Karapurkar, T., Doernberg, N., Boyle, C. *et al.* (2003). Prevalence of autism in a US metropolitan area. *JAMA*, **289** (1), 49–55.
- You, X., Norr, M., Murphy, E., Kuschner, E.S., Bal, E. *et al.* (2013). Atypical modulation of distant functional connectivity by cognitive state in children with autism spectrum disorders. *Frontiers in Human Neuroscience*, **7**, 482.
- Ypma, R.J., Moseley, R.L., Holt, R.J., Rughooputh, N., & Floris, D.L. *et al.* (2016). Default mode hypoconnectivity underlies a sex-related autism spectrum. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*.
- Zang, Y., Jiang, T., Lu, Y., He, Y., & Tian, L. (2004). Regional homogeneity approach to fMRI data analysis. *NeuroImage*, **22** (1), 394–400.

Received: 1 May 2015

Accepted: 28 May 2016