

## Functional Connectivity

### Definition

*Functional connectivity* (FC) has been defined as “temporal correlations between spatially remote neurophysiological events” (Friston, Frith, & Frackowiak, 1993), a definition that is still considered authoritative today. The reference to correlation highlights the distinction from the concept of *effective connectivity*, which invokes causality and has been defined as “the influence one neural system exerts over another” (Friston et al., 1993). Correlations can exist on widely differing time scales, specifically high frequencies in the gamma band (> 25 Hz), as detected in electroencephalography (EEG) and magnetoencephalography (MEG), and low frequencies (< 0.1 Hz) in functional connectivity MRI (fcMRI). A more encompassing recent definition of FC refers to “the statistical dependence between remote neural processes” (Honey, Kotter, Breakspear, & Sporns, 2007).

### Historical

In the first FC study of ASD, Horwitz et al. (1988) used positron emission tomography (PET) to examine the correlations of glucose metabolic rates between numerous brain regions of interest (ROIs). Correlations were reduced in young men with ASD for ROI pairings within and between frontal, parietal, subcortical, and cerebellar ROIs. This early interest in connectivity was stimulated by later findings of atypical white matter growth patterns in children with ASD (Courchesne et al., 2001), which may suggest early-onset axonal anomalies. It is also consistent with a view of ASD as a disorder of functional networks, rather than one or a few local sites (Belmonte et al., 2004; R-A Müller, 2007; Rippon, Brock, Brown, & Boucher, 2007).

### Current knowledge

#### *Underconnectivity theory*

Recent interest in FC was prompted by a study by Just et al. (2004), who reported that correlations of the blood oxygen level dependent (BOLD) fMRI signal during sentence comprehension were reduced between multiple ROIs in participants with ASD (compared to a typically developing [TD] control group matched for age, but not handedness). The “underconnectivity theory”, as proposed by these authors, has found support in a large number of subsequent studies that examined FC for finger movement (Mostofsky et al., 2009; Villalobos, Mizuno, Dahl, Kemmotsu, & Müller, 2005), face processing (Kleinhans et al., 2008), verbal working memory (Koshino et al., 2005), sentence comprehension (Kana, Keller, Cherkassky, Minshew, & Just, 2006), response inhibition (Kana, Keller, Minshew, & Just, 2007; Lee et al., 2009), embedded figures (Damarla et al., 2010), problem solving (Just, Cherkassky, Keller, Kana, & Minshew, 2007), cognitive control (Solomon et al., 2009), self-representation (Lombardo et al., 2010), and tasks tapping into theory of mind (Kana, Keller, Cherkassky, Minshew, & Adam Just, 2009; Mason, Williams, Kana, Minshew, & Just, 2008). General underconnectivity has in fact been presented as a potential “first firm finding” in ASD (Hughes, 2007). The evidence is further strengthened by associations between reduced FC and other markers of neurological, cognitive, or diagnostic abnormality in ASD. For example, two studies observed a correlation between fronto-parietal FC and size of the callosal genu in adults with ASD that was not seen in control participants (Just et al., 2007; Kana et al., 2006). Kleinhans et al. (2008) found that reduced FC between fusiform face area and amygdala was associated with symptom severity on the ADOS Social score (Lord, Rutter, DiLavore, & Risi, 1999) in adults with ASD. Association between reduced fronto-parietal connectivity and attention deficit was observed by Solomon et al. (2009) in adolescents with ASD. One recent study (Dinstein et al., 2011) found reduced interhemispheric synchronization of activity in language-related brain regions (inferior frontal and superior temporal gyri) in toddlers with ASD scanned during natural sleep. Inferior frontal synchronization was correlated with an expressive language score.

#### *Partial overconnectivity*

Often overlooked is the fact that in the original study by Just et al. (2004), reduced correlations were detected in only 10 out of 186 ROI pairs. In addition, a number of studies have reported results that appear inconsistent with the

underconnectivity theory. Welchew et al. (2005) examined BOLD correlations for a large matrix of 90 cortical and subcortical ROIs. Although they focused on reduced connectivity in the medial temporal lobe in adults with high-functioning autism or Asperger’s syndrome, they also detected many ROI pairs that showed greater FC in ASD compared to a TD control group. Subsequent studies presented findings on FC of thalamus (Mizuno, Villalobos, Davies, Dahl, & Müller, 2006) and caudate nucleus (Turner, Frost, Linsenhardt, McIlroy, & Müller, 2006) that suggested diffusely increased FC in ASD, also inconsistent with the underconnectivity theory. One of these (Mizuno et al., 2006) and a further study on cortico-cortical connectivity of networks related to source memory (Noonan, Haist, & Müller, 2009) suggested that effects of apparent “overconnectivity” in ASD were characterized by widespread low-threshold correlations (‘noisy connectivity’) not seen in control groups. A few other recent studies observed overconnectivity or mixed findings (underconnectivity between some regions, overconnectivity between others) in adults and adolescents with ASD related to imitation (Shih et al., 2010), emotional processing (Ebisch et al., 2011; Wicker et al., 2008), and the default mode network (Monk et al., 2009). One further study (Shih et al., 2011) found that overconnectivity of posterior superior temporal sulcus, which plays a role in biological motion perception, face processing, joint attention, auditory-visual integration, and language perception (Redcay, 2008), was associated with reduced functional differentiation within this region in children and adolescents with ASD.

#### *Resting state and the default mode network*

The study by Monk and colleagues (2009) mentioned above belongs to a growing literature on FC associated with task-free resting states in ASD. Cherkassky et al. (2006) reanalyzed resting blocks (fixation cross only) from several task-activation studies in 12 ROIs attributed to the default mode network (DMN) and found underconnectivity for an overwhelming majority of ROI pairs in young adults with ASD. Kennedy et al. (2008) acquired continuous resting state fMRI data for seven minutes and found that averaged correlation maps for three seeds considered nodes of a task-negative network (equivalent to the DMN) were strongly reduced in adolescents and adults with ASD, overall consistent with the findings by Cherkassky et al. On the other hand, FC within a task-positive network (regions that frequently activate across different task domains) was similar between ASD and TD groups, and differences in effects also included some connectivity clusters seen only in the ASD, but not in the TD group. Monk et al. (2009), using only a single seed in posterior cingulate cortex (PCC), found more mixed results of partial under- and overconnectivity within the DMN in adults with ASD. These authors also found that impaired social functioning (from the ADI-R; Rutter, Lord, & LeCouteur, 1995) was associated with reduced connectivity between PCC and medial prefrontal regions and that restricted and repetitive behaviors from the same measure were positively correlated with connectivity between PCC and right parahippocampal gyrus. In a subsequent study, the same group (Wiggins et al., 2011) found that posterior regions of the DMN, as detected in data-driven self-organizing maps for each individual participant, had reduced FC with two right-hemispheric inferior parietal and superior frontal sites. Another study examining default mode networks derived from independent component analysis identified several sites in frontal and parietal lobes where reduced connectivity was associated with symptom severity in adolescents and young adults with ASD (Assaf et al., 2010). Resting state data have also been applied to questions other than the DMN. Anderson et al. (2011) investigated the BOLD signal correlation between each brain voxel and the homotopic voxel in the contralateral hemisphere and found interhemispheric underconnectivity in adolescents and young adults with ASD in several perisylvian and parietal regions. Ebisch et al. (2011) used the insula, considered a crucial area for “emotional awareness”, as fMRI seed and reported several sites with reduced connectivity, such as amygdala and PCC.

#### *Methodological issues*

While a clear majority of fMRI studies in ASD have reported findings in support of the underconnectivity theory, relatively little attention has been paid to methodological questions in the context of partially inconsistent results. Thai et al. (2009) raised methodological concerns regarding the potential impact of task factors and increased variability in ASD cohorts. In a comparative methodological fMRI study, Jones et al. (2010) indeed showed that underconnectivity effects in ASD (compared to a matched TD group) almost completely disappeared when modeled task effects were regressed out (see below). This study further suggested that inverse findings of overconnectivity in ASD might be related to global signal regression, which relates to a recent discussion in the fMRI methods literature about the treatment of global signal fluctuations (i.e., changes in signal intensity seen across the whole

brain). While it is generally accepted that some of these BOLD fluctuations may be noise, it has been argued that their removal through global signal regression results (by mathematical necessity) in potentially spurious anti-correlations (Murphy, Birn, Handwerker, Jones, & Bandettini, 2009). It is further likely that some components in the global signal may actually reflect true neuronal fluctuations (Fox, Zhang, Snyder, & Raichle, 2009; Schölvinck, Maier, Ye, Duyn, & Leopold, 2010)

A recent survey of 32 fMRI studies in ASD published by late 2010 (R.-A. Müller et al., 2011), however, showed that global signal regression alone is unlikely to explain differences in FC findings on ASD described above. This survey suggested that studies were most likely to generate underconnectivity findings in ASD when task effects were not regressed out, data were not low-pass filtered, and results were considered only for task-related ROIs (rather than the whole brain). Removal of task effects and low-pass filtering is related to the concept of *intrinsic connectivity* (Van Dijk et al., 2010), which refers to low-frequency (< 0.1 Hz) fluctuations in the BOLD signal that may reflect fluctuations in local field potentials (Leopold, Murayama, & Logothetis, 2003; Schölvinck et al., 2010). These fluctuations are spontaneous (i.e. independent of online cognitive, task-related processing) and have been related to Hebbian plasticity and the sculpting of neuronal connections based on long-term experience (Lewis, Baldassarre, Comitteri, Romani, & Corbetta, 2009; Sadaghiani, Hesselmann, Friston, & Kleinschmidt, 2010). It is remarkable that many ASD studies that were fully adapted to isolating such intrinsic connectivity through task regression and low-pass filtering yielded evidence incompatible with the underconnectivity theory, whereas many studies in support of underconnectivity examined task-activation effects or a mixture of such effects and intrinsic fluctuations (for details, see R.-A. Müller et al., 2011).

#### *Electrophysiological studies*

Although EEG and MEG can detect signal correlations in a much wider frequency range than fMRI due to their superior temporal resolution, the current EEG and MEG literature on FC in ASD remains surprisingly small. Several studies have examined the temporal coherence of EEG or MEG signals. Coherence in the gamma band is considered to reflect binding during perceptual processing across brain regions (Nase, Singer, Monyer, & Engel, 2003; Roelfsema, Engel, Konig, & Singer, 1997), presumably based on axonal connectivity. Several studies in children and adults with ASD suggest abnormalities in gamma band activity related to face perception (Grice et al., 2001), viewing of illusory shapes (Brown, Gruber, Boucher, Rippon, & Brock, 2005), and auditory perception of clicks (Wilson, Rojas, Reite, Teale, & Rogers, 2007), arguably reflecting impaired perceptual binding. Interhemispheric coherence of visual evoked potentials was reduced in a small sample of children with ASD (Isler, Martien, Grieve, Stark, & Herbert, 2010), but this effect was found only in theta and lower bands (< 8 Hz), not in the gamma band.

However, not all studies have reported results consistent with underconnectivity. One EEG study (Orekhova et al., 2007) found atypically increased spectral power in the gamma band for task-free visual conditions, which was correlated with developmental delay in boys with ASD aged 3-8 years. Murias et al. (2007) examined EEG coherence during rest, with complex findings grossly suggesting decreased long-distance and increased short-distance connectivity (especially in temporal lobes) in adults with ASD for frequency bands between 3 and 17 Hz (see also Bartfeld et al., 2011 for partially consistent results). Conversely, an EEG study of adults with ASD during REM sleep reported reduced short-distance right frontal coherence in the theta band, but increased long-distance left fronto-occipital coherence in the delta band (Léveillé et al., 2010).

A few studies have used alternative approaches to investigate FC in ASD. Pollonini et al. (2010) used Granger causality and graph theory to analyze resting state MEG data from a small sample of young adults with ASD, reporting an atypically increased characteristic path length, which refers to the number of edges [grossly equivalent to causal links] that must be traversed to go from one node [grossly equivalent to a brain region] to another (Bullmore & Sporns, 2009). An additional finding was a reduced clustering coefficient in ASD, i.e. a reduction in tightly interconnected local clusters of nodes. Both of these findings were replicated in a resting state EEG study using graph theory by Bartfeld et al. (2011). Overall, these findings suggest that a typical ‘small-world’ architecture, in which efficient connectivity is achieved by strong local clustering of connections balanced with long-distance connections between hubs (Bullmore & Sporns, 2009), may be impaired in ASD (Bartfeld et al., 2011).

In summary, the electrophysiological literature tentatively suggests impaired FC in ASD as well as general aberrations of the typical modular ‘small world’ organization of networks.

## Future directions

Whereas the EEG and MEG literature remains limited, the fMRI literature in ASD has grown rapidly in recent years. However, the quantity of fMRI findings has not always been matched by the quality of methods. Sharpened methodological awareness will be crucial for a better interpretation of fMRI findings in ASD. An exemplary issue concerns head motion. The vast majority of fMRI studies in ASD did not test for group differences in head motion, although it is known that head motion is likely to affect the interregional correlation of the BOLD signal (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012). As indicated earlier, several other methodological choices may crucially affect the pattern of connectivity disturbances observed in ASD that may be grossly characterized as general underconnectivity vs. partial overconnectivity (R.-A. Müller et al., 2011). fMRI studies directly testing the impact of differing processing pipelines will contribute to a more precise understanding of FC in ASD. At present, a tentative interpretation of the literature would suggest that BOLD correlations tend to be reduced in ASD when task-activated data (or data from uncontrolled cognition during resting states) are examined for ROIs identified based on expected or known activation in the TD population. On the other hand, BOLD correlations are often found to be atypically increased outside such domain-specific networks, especially if time series are low-pass filtered and effects of task are removed in order to isolate intrinsic low-frequency BOLD fluctuations that are thought to best reflect functional network organization (Cordes et al., 2001; Fox & Raichle, 2007).

Assuming that such an interpretation holds generally true in light of future methodologically more rigorous studies, results from both types of fMRI studies may actually reflect interesting and complementary aspects of network dysfunction in ASD. The emergence of network connectivity can be understood with respect to the interplay between experience-driven constructive and regressive processes (Johnson, 2011; Kandel, Jessell, & Sanes, 2000). Within-network underconnectivity, observed in many task-related studies, may reflect disturbances in the constructive processes of synaptic stabilization and axonal myelination. On the other hand, out-of-network diffuse overconnectivity, as seen in some intrinsic fMRI studies, may reflect disturbances of synaptic pruning due to diminished interactive experience related to the autistic condition itself, or traces of early white matter overgrowth in ASD (Courchesne et al., 2001). Forthcoming diffusion tensor imaging (DTI) studies better characterizing the axonal organization associated with early overgrowth in infants and toddlers will be instrumental in answering this latter question (for first findings, see Weinstein et al., 2011; Wolff et al., 2012).

Aside from improved awareness of methodological implications in future fMRI studies, other techniques will be instrumental for a comprehensive picture. As mentioned, more electrophysiological studies with larger sample sizes will be important for examining FC in higher frequency bands. In addition, DTI advances may allow investigations to expand beyond the gross impairment of large fiber tracts, which has been well documented for ASD participants above 8 years of age (Alexander et al., 2007; Fletcher et al., 2010; Shukla, Keehn, & Müller, 2011), towards the detection of potential anatomical overconnectivity that may, for example, be reflected in increased presence of crossing fibers (cf. (Lange et al., 2010). Multimodal approaches (e.g., combining fMRI and DTI with EEG or MEG) promise to be more powerful than single-technique studies that have been common in the literature.

## Acknowledgments

This review was supported by the National Institutes of Health (R01-DC006155, R01-MH081023). Thanks to Chris Keown and Brandon Keehn for helpful comments on content and style of earlier drafts.

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