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Distortions and disconnections: Disrupted brain connectivity in autism

Sam Wass *

Centre for Brain and Cognitive Development, School of Psychology, Birkbeck College, Malet Street, London WC1E 7HX, United Kingdom

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ABSTRACT

The past few years have seen considerable interest in findings of abnormal brain connectivity in the autism spectrum disorders (ASD). We review recent work from neuroimaging and other sources, and argue that there is considerable convergent evidence suggesting that connectivity is disrupted in ASD. We point to evidence both of local over-connectivity and of long-distance under-connectivity, and describe some non-uniformities in this picture, most notably that disruptions appear more severe in later-developing cortical regions. We conclude by discussing a number of extant questions. Firstly, we consider whether aberrant connectivity should be seen as part of the primary pathogenesis of autism, or whether disrupted connectivity in ASD emerges over time. Secondly, we consider how the patterns of disrupted connectivity found in ASD might relate to those being found in a range of other disorders.

1. Introduction

1.1. Connectivity and ASD – a brief history

The autism spectrum disorders (ASD) are neurodevelopmental disorders characterized by deficits in social interaction, communication, and stereotyped or repetitive behaviors (APA, 1994). Although the first report of functional under-connectivity in ASD came from Horwitz, Rumsey, Grady, and Rapoport (1988) it is only in recent years that the study of connectivity in ASD has attracted widespread attention (although see also Brock, Brown, Boucher, & Rippon, 2002; Carpenter et al., 2001; Castelli, Frith, Happe, & Frith, 2002; Rubenstein & Merzenich, 2003). Just, Cherkassky, Keller, and Minshew (2004) provided an influential formulation of what they dubbed "under-connectivity theory", arguing that "autism is a cognitive and neurobiological disorder marked and caused by under-functioning integrative circuitry that results in a deficit of integration of information at the neural and cognitive levels". In recent years, under-connectivity theory has attracted considerable attention as a number of studies have reported lower than expected between-region functional correlations on a range of tasks (e.g. Koshino et al., 2008), and DTI has revealed markers of disordered structural connectivity in individuals with ASD (e.g. Sundaram et al., 2008).

Belmonte et al. (2004) provided an important addendum to the Just et al. paper. They noted that whereas some authors discuss ASD as a problem of *under*-connectivity (Brock et al., 2002; Just et al., 2004), others treat the problem as one of *over*-connectivity (e.g. Rubenstein & Merzenich, 2003). Belmonte et al. reconciled these two ideas, suggesting that "high local connectivity may develop in tandem with low long-range connectivity" and that "high physical connectivity and low computational connectivity may reinforce each other by failing to differentiate signal from noise" (see also Johnson, 2005; Quartz & Sejnowksi, 1997; Rubenstein & Merzenich, 2003).

1.2. Connectivity and ASD – the hypothesized link to behavior

Long-distance under-connectivity in ASD implies that "any facet of psychological 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). "Core" autistic deficits in social interaction, language and repetitive and restrictive behaviors (APA, 1994) arise because these are the domains that place the largest demands on the time-sensitive integration of information from spatially discrete brain areas (Herbert, 2005; Just et al., 2004; Lewis & Elman, 2008; although see Mottron, Dawson, Soulieres, Hubert, & Burack, 2006). As such, the theory is in some ways a neural substantiation of central coherence theory (e.g. Happe, 1999; Happe & Frith, 2006) which posits "a cognitive style biased towards local rather than

* Fax: +44 20 7631 6258.
E-mail address: samwass@gmail.com

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global information processing" (Happe, 1999), although Just et al. (2004) contest this claim, pointing out that central coherence theory postulates "a core deficit in central processing" (Happe & Frith, 2006) whereas "under-connectivity theory treats the coherence as an emergent property of the collaboration among brain centers" (Just et al., 2004).

Local over-connectivity has also been connected to findings of behavioral hyper-specificism and inferior generalization in ASD (Casanova et al., 2006a; Cohen, 2007; see also Gustafsson, 1997; McClelland, 2000), and to superior discrimination on certain tasks (Cohen, 2007; see also Mottron et al., 2006 for an excellent discussion of this), as for example in the embedded figures task (see also Plaisted, O'Riordan, & Baron-Cohen, 1998; Shah & Frith, 1983).

1.3. What is connectivity...

Friston (1994) suggested that there are two guiding principles to neural function. The first is *functional segregation* and the second is *functional integration*, a process mediated by connectivity. Functional segregation describes the location of information processing; as Friston notes, the explosion of neuroimaging work over the last twenty years "has been extremely successful in establishing functional segregation as a principle of organization in the human brain" (Friston, 1994). The aspect that has received relatively less attention is the functional integration of information – how information is combined between different areas during the performance of particular tasks (Friston, 1994; Honey et al., 2009; Horwitz, 2003).

In this article we will distinguish two types of connectivity (following Friston, 1994; Horwitz, 2003; Sporns, 2007):

Structural connectivity refers to the physical or structural (synaptic) connections linking sets of neurons or neuronal elements, and to their associated structural biophysical attributes encapsulated in parameters such as synaptic strength or effectiveness (Friston, 1994; Sporns, 2007). Structural connectivity can describe how individual neurons are connected (at the micro scale) and also how different brain regions are connected (at the macro scale).

Functional connectivity refers to the degree to which activity in one area correlates with activity in another (David, Cosmelli, & Friston, 2004; Friston, 1994), or to the temporal synchronization of activation of two brain areas during task performance (Friston, 1994; Horwitz, 2003; Rippon, Brock, Brown, & Boucher, 2007). As a purely correlative measure, measurements of functional connectivity leave open questions of causation, and of whether control is symmetric, asymmetric, or coordinated by a third area (c.f. effective connectivity – Friston, 1994, 2009).

It is important to recognize that structural and functional connectivity are not necessarily co-referential. For example, tonic neuromodulatory changes can affect the functional activation patterns of a range of neurons without altering the structural connectivity (Friston, 1994; see also He, Snyder, Zempel, Smyth, & Raichle, 2008; Honey et al., 2009; Sorg et al., 2007; Sporns, 2007; Sporns, Tononi, & Edelman, 2000; Stephan, Friston, & Frith, 2009).

1.4. ... and how do we measure it?

1.4.1. Structural connectivity

The past few years have seen an explosion in interest in the tools that can be used to study brain connectivity (Friston, 2002; Honey et al., 2009; Horwitz & Glabus, 2005). Structural connectivity is being measured using MRI-based techniques such as diffusion tensor imaging (DTI) (Behrens et al., 2003; Conturo et al., 1999; see Karlsgodt et al., 2008 for an excellent brief summary) that examine the structural integrity of white matter tracts that are seen as the inter-areal macro structural correlates of brain connectivity (Fields, 2008; Oishi et al., 2008; although this may be a simplistic view – see e.g. Karadottir, Hamilton, Bakiri, & Attwell, 2008; Schummers, Yu, & Sur, 2008; Ziskin, Nishiyama, Rubio, Fukaya, & Bergles, 2007). Tractography based on DTI (e.g. Hagmann et al., 2003; Hagmann et al., 2008; Lewis, Theilmann, Sereno, & Townsend, 2009) can be used to trace fiber tracts, allowing association fiber pathways to be mapped *in vivo*. Problems remain with these techniques, though, particularly coping with multiple fiber orientations within a single voxel (Wedeen et al., 2008).

At the macro (whole brain) level, structural MRI has also been used to look at correlations between the size of different brain regions (e.g. Boucher et al., 2005), and a number of other techniques have also been used to aid the parcellation of structural MRI data, including voxel-based morphometry (VBM), a *post hoc* analysis that allows the relative volumes of different brain areas to be compared with greater precision than traditional morphometric techniques (e.g. Abell et al., 1999).

At a much higher spatial resolution, *post mortem* histological analyses (e.g. Casanova et al., 2006a) can trace neural connectivity at the micro- and meso-levels (such as mini-columnar structures), although sample sizes, particularly of immature subjects, remain (thankfully) very low.

1.4.2. Functional connectivity

Functional connectivity data on fMRI comes from studying correlations between activation patterns of particular voxels during task performance. EEG has been used to provide indices of connectivity in ASD in two ways – firstly, power in the higher frequency bands (particularly gamma, typically >25 Hz), that is thought (e.g. Csibra, Davis, Spratling, & Johnson, 2000; Engel & Singer, 2001; Paik, Kumar, & Glaser, 2009) to represent binding between spatially discrete areas of the brain (see e.g. Rippon et al., 2007; Thai, Longe, & Rippon, 2009). Secondly, coherence, which gives an index of the average degree of correlation between spatially discrete electrode groupings (see e.g. Lachaux, Rodriguez, Martinerie, & Varela, 1999; Murias, Webb, Greenson, & Dawson, 2007; Thatcher, North, & Biver, 2008).

For both fMRI and EEG, more advanced techniques have recently been developed that allow the calculation of effective connectivity – the influence that one neural system exerts over another (Friston, 1994, 2009; Sporns, 2007). These techniques, which include Granger causal modeling and dynamic causal modeling (see Friston, 2009 for a review) have not, to our knowledge, been applied to data from subjects with autism.

It is also interesting to note that some ingenious behavioral measures have been interpreted as evidence of abnormal functional connectivity. For example, Tommerdahl, Tannan, Holden, & Baranek, 2008 (see also Haswell, Izawa, Dowell, Mostofsky, & Shadmehr, 2009) investigated the absence of stimulus-driven synchronization effects on tactile perception in autism, a finding they suggest may relate to macro-columnar under-connectivity in the somatosensory cortex. Again, a full discussion of this work is beyond the scope of this review.

Finally, neural network modeling – which can model both structural and functional aspects – has played an important role in investigating how disrupted connectivity might affect subsequent autistic development at a variety of spatiotemporal scales (e.g. Noriega, 2008).

1.4.3. Other techniques

In addition to those areas we discuss in this paper, there has also been considerable discussion of the micro-structural correlates of connectivity, such as neurite morphology and synaptogenesis (see, for example, Persico & Bourgeron, 2006), signaling molecules such as HGF/MET, Reelin and neurotrophins (see e.g. Pardo & Eberhart, 2007), synaptic proteins (e.g. neuroligins – see Garber, 2007; Gutierrez et al., 2009) and neuro- and/or gliogensis

(see e.g. Courchesne et al., 2007; McCaffery & Deutsch, 2005). A number of authors have also discussed the role that disruptions to various neurotransmitters (in particular GABA) might play during development (Delong, 2007; Kana, Keller, Minshew, & Just, 2007; van Kooten et al., 2005).

A full review of this material would render this paper indigestibly large; the interested reader is recommended to visit a number of excellent recent discussions on these subjects. Particular highlights include Courchesne et al. (2007, on the micro-structural correlates of early brain overgrowth), Herbert (2005, also on the mechanisms that might drive brain overgrowth), Pardo and Eberhart (2007, on how the micro correlates of structural connectivity might become disrupted as a result of aberrant development) and Persico and Bourgeron (2006, also on the micro correlates of disrupted structural connectivity).

1.5. Outline of what is to come

In Sections 2–4 of this article we review recent evidence regarding connectivity in ASD. For the sake of clarity, we have structured our discussion around three principal hypotheses. In each section, we review the evidence from a variety of methodologies that can be brought to bear in addressing each hypothesis.

2. Hypothesis 1 – under-connectivity exists within large-scale networks in ASD

2.1. Evidence from fMRI

A number of studies have used fMRI to identify medium- and long-distance functional under-connectivity in individuals with ASD (see Müller, 2008; Williams & Minshew, 2007 for more specialized recent reviews). Horwitz et al. (1988), using PET, provided the first such finding, specifically a lower level of correlation in activation between frontal, parietal, and other regions in a resting adult autistic brain. Using fMRI, Just et al. (2004) found reduced functional connectivity between Broca's area, Wernicke's area and the dorsolateral pre-frontal cortex on a sentence comprehension task. Kleinhans et al. (2008) have described functional disconnections within the social brain network: reduced functional connectivity between the Fusiform Face Area (FFA) and the left amygdala, posterior cingulate and thalamus on a face processing task. Other studies have found various regions to be "functionally under-connected" using, for example, visuomotor tasks (V1 and inferior frontal cortex – Villalobos, Mizuno, Dahl, Kemmotsu, & Müller, 2005; also Mostofsky et al., 2009), working memory for faces (inferior left pre-frontal, right posterior temporal and fusiform area – Koshino et al., 2008), emotion recognition (medial temporal lobe and other cortical structures – Welchew et al., 2005), response inhibition (anterior cingulate gyrus, middle cingulate gyrus, insula, parietal and premotor regions – Kana et al., 2007), executive planning tasks (frontal and other areas – Just, Cherkassky, Keller, Kana, & Minshew, 2007; also Solomon et al., 2009) and in a resting state (Cherkassky, Kana, Keller, & Just, 2006).

Only a small number of studies have provided evidence that appears inconsistent with a model of globally reduced long-range connectivity between brain regions. Mizuno, Villalobos, Davies, Dahl, & Müller, 2006, for example, measured fMRI during simple visuomotor coordination and found increased subcortico-cortical connectivity in subjects with ASD relative to controls. Monk et al. (2009) found that widespread under-connectivity within the default mode network was accompanied by increased connectivity between the posterior cingulate cortex and right temporal lobe and right parahippocampal gyrus.

Despite the profusion of studies that have found evidence for under-connectivity within large-scale networks in ASD, there is one important limitation to many of these studies: they have all looked for correlations between relatively small numbers of regions of interest (ROIs), that form specific "expected" functional networks. This leaves us vulnerable to missing other abnormalities. For example, Welchew et al. (2005) measured functional connectivity between 90 ROIs during incidental processing of fearful emotions, and found specific long-range under-connectivity between "expected" nodes (primarily functional disconnection of the temporal lobe) was accompanied by a wider pattern of *higher*-than-expected long-range connectivity between areas where functional activation was "unexpected" (see also Müller, 2008).

2.2. Evidence from EEG/MEG

2.2.1. Power

A number of groups have also reported findings of *decreased* induced gamma power in response to particular stimuli, interpreted as a failure to combine neural firing in response to particular stimuli (Rippon et al., 2007). For example, Elsabbagh et al. (2009) found that 10-month-old ASD siblings showed decreased induced gamma band activity in response to direct gaze. Similarly, Wilson, Rojas, Reite, Teale, and Rogers (2007) used magnetoencephalography (MEG) on 7–17-year-old subjects with ASD and found significantly reduced left (but not right) hemispheric gamma (40 Hz) power 200–500 ms after the onset of auditorily presented clicks (see also Grice et al., 2001; although Brown, Gruber, Boucher, Rippon, & Brock, 2005 report an apparently contradictory finding).

2.2.2. Coherence

Coben, Clarke, Hudspeth, and Barry (2008) measured resting state EEG coherences in 6–11-year-old subjects with ASD, and reported reduced intra-hemispheric coherences in delta (1.5–3.5 Hz) and theta (3.5–7.5 Hz), with group differences equally acute for short-medium and long-distance electrode pairs. Inter-hemispheric coherences were also extensively reduced in the ASD group, across a variety of frequency bands. Testing 7–16-year-old subjects with ASD, and using phase synchrony analysis based on MEG, Velazquez et al. (2009) reported apparently similar results: extensively reduced coherences in the ASD group across a number of long- and medium-distance electrode pairs (26 Hz and 32 Hz).

Murias et al. (2007) also measured resting state coherences in adults with ASD. They also found reduced coherences, but only in the lower alpha (8–10 Hz) range; these were marked over long-distance electrode pairs across the whole brain, and across shorter-distance electrode pairs in the frontal region. It should be noted, however, that these findings of reduced long- and medium-range coherence are not found across all frequencies. Murias et al. (2007) reported that, when all electrode pairs >3 cm apart were averaged together, subjects with ASD showed globally lower alpha (8–10 Hz) coherences but globally *increased* theta (3–6 Hz) coherences (Murias et al., 2007 – Fig. 1. See also Cantor, Thatcher, and Kaye (1987)).

2.3. Evidence from DTI/structural MRI

Studies using structural MRI techniques (including VBM) have reported reductions in the size of the corpus callosum in children and adults with ASD (see Frazier & Hardan, 2009 for a meta-analysis). In some studies, the decrease is found relative to total brain volume (Boger-Megiddo et al., 2006; Keary et al., 2009; Vidal et al., 2006), whereas in other cases there is an absolute decrease in corpus callosum area independent of brain volume (Egaas, Courchesne, & Saitoh, 1995; Manes et al., 1999). Some studies have

reported changes to be particularly acute in anterior areas of the corpus callosum (Keary et al., 2009; Lewis et al., 2009; Waiter et al., 2005), although this finding is inconsistent. Studies using DTI on children and adults have also reported reduced volume and increased diffusion in the corpus callosum (Alexander et al., 2007), as well as lower FA in both the corpus callosum (Barnea-Goraly et al., 2004; Kumar et al., 2009) and near-by areas (Keller, Kana, & Just, 2007; Kumar et al., 2009).

However, others findings are at odds with these. Using DTI and high b value diffusion-weighted imaging (DWI), Ben Bashat et al. (2007) reported *no* structural changes in the corpus callosum in a small 1.8–3.3-year-old sample ($N = 7$; see also Herbert et al.,, 2004).

The explanation for the difference between the majority of studies and the (small-sample) Ben Bashat study may be methodological. But it may also be a result of the younger age range of his sample – for comparison, the participant age ranges were 7–33-year-old for Alexander et al. (2007), 10–35-year-old for Keller et al. (2007) and 11–18-year-old for Barnea-Goraly et al. (2004). The one structural MRI study conducted on toddlers with ASD (aged 3–4-year-old) also found no difference in absolute corpus callosal volume compared to TD, although subtler differences emerged when corrections for total cerebral volume were made (Boger-Megiddo et al., 2006). Again, longitudinal studies are necessary to track possibly vital developmental trends here.

2.4. Brain overgrowth and long-distance under-connectivity

One finding that has dominated the developmental neurobiological and computational literature on connectivity in ASD in recent years is the finding of abnormally accelerated brain growth (defined as 1.5 S.D.s above the norm) in c.70% of children with ASD during the first 2 years of life (Dawson et al., 2007; Herbert, 2005; Lainhart, 2006; Redcay & Courchesne, 2005). This appears in many individuals to stop abruptly at around 2–3 years; by adolescence, the group mean brain volume is comparable between typically developing and autistic individuals (Redcay & Courchesne, 2005).

It is important to note that it does not necessarily follow that abnormal brain growth trajectories will lead to abnormal-connectivity. However, several authors have noted that a faster-grown brain might tend toward different optimal connectivity patterns (Braitenberg, 2001; Chklovskii, Schikorski, & Stevens, 2002; Jäncke, Staiger, Schlaug, Huang, & Steinmetz 1997; Ringo, Doty, Demeter, & Simard, 1994; Sporns & Zwi, 2004). This idea springs from cross-species (Braitenberg, 2001; Frahm, Stephan, & Stephan, 1982; Rilling & Insel, 1999; Zhang & Sejnowski, 2000) and cross-gender (Luders, Narr, Zaidel, Thompson, & Toga, 2006) work suggesting that larger brains have a relatively higher proportion of short-distance (intra-hemispheric) to long-distance (inter-hemispheric) connectivity. (Although the picture emerging from recent developmental DTI work is considerably more complicated than this (Hasan et al., 2008, 2009)).

Lewis and Elman (2008; see also Lewis et al., 2009) built a connectionist model in which the total number of neurons and connections was kept constant, and growth was simulated by increasing the conduction delay between neurons (calculated as a function of the physical length of the connections (derived from head circumference) and conduction velocity (derived as a function of developmental increases in axon diameter and myelination)). They found that a faster grown network tended to be less disrupted by the subsequent removal of inter-hemispheric connections, indicating a reduced reliance on long-distance connections. A larger brain tends to rely more on local- than on long-distance connections because local connections are relatively cheaper, both computationally (Lewis & Elman modeled conduction delays) and physically: in a larger brain, long-distance connections require relatively more resources to build (Courchesne & Pierce, 2005b; Ringo et al., 1994; Zhang & Sejnowski, 2000; see also Sporns & Zwi, 2004).

2.5. Conclusion

In this section, we have reviewed convergent evidence from fMRI (2.1) and EEG (2.2) that is heavily suggestive of long- and medium-distance under-connectivity in ASD. We did, though, note one common limitation of the fMRI studies, which is that they tend only to report on connectivity between a small number of ROIs within "expected" functional networks, thus possibly missing important findings of over-connectivity between regions that are not "expected" to be connected (see Welchew et al., 2005). There are also important between-region trends that have been revealed by these studies, that we discuss further in Section 4.

With regard to structural connectivity (2.3), there is also considerable evidence of disruption to inter-hemispheric white matter structures. However, two smaller studies using younger (1.8–4-year-old) subjects reported milder or non-existent disruption. This leaves open the possibility that connectivity disruptions may emerge over developmental time. With regard to intra-hemispheric white matter the picture is considerably more complicated, as we discuss further in Section 3.3.

3. Hypothesis 2 – over-connectivity exists within local networks in ASD

3.1. Evidence from fMRI

In addition to the findings of medium- to long-range functional under-connectivity discussed in Section 2, a smaller number of fMRI studies have reported what appears to be evidence of local functional over-connectivity: that functional activation *within certain brain areas* is more than usually correlated with activity within the same region (see also Belmonte & Yurgelun-Todd, 2003; Belmonte et al., 2004; Rubenstein & Merzenich, 2003). For example, Schmitz et al. (2006) reported increased activation in the left inferior and orbital frontal gyrus during a motor inhibition task, within the left insula during an interference-inhibition task and within the parietal lobes during a set shifting task (see Baron-Cohen et al., 1999; Belmonte & Yurgelun-Todd, 2003; Manjaly et al., 2007 for similar findings in other domains). Using voxel-based morphometry (VBM), Schmitz et al. (2006) noted a correlation between increased frontal gray matter density and increased functional activation within that area. However, these fMRI findings are comparatively much rarer than those of medium- to long-range functional under-connectivity.

3.2. Evidence from EEG

3.2.1. Power

Elsabbagh et al. (2009) reported increased resting state gamma (20–60 Hz) activity in central and right temporal regions in 10-month-old ASD siblings. Also using a resting state paradigm, Orekhova et al. (2007) reported more high-frequency activity (gamma – 25–70 Hz) in 3–8-year-old children with ASD. They subsequently found gamma power to correlate with lower suppression of the P50, an ERP marker that they suggest is associated with low- but not high-functioning subjects with ASD (Orekhova et al., 2007). Findings of increased gamma power have been interpreted as evidence of a surfeit of resting state connectivity (e.g. Rippon et al., 2007; c.f. Kennedy, Redcay, & Courchesne, 2006 for an analogous fMRI-based finding).

3.2.2. Coherence

In addition to the findings of reduced resting state coherences in the lower alpha (8–10 Hz) range over long-distance electrode pairs (and short-distance electrode pairs in the frontal region) reported in Section 2, Murias et al. (2007) also found *increased* coherences in the theta (3–6 Hz) frequency band, particularly marked in short-distance frontal and left temporal electrode pairs (although as noted in Section 2, these findings are different at different bands). Similarly Velazquez et al. (2009), in addition to the reduced coherences reported in Section 2, also found locally elevated coherences within parietal areas.

3.3. Evidence from DTI/structural MRI

In an influential and much discussed early study in this field, Herbert et al. (2004; discussed in Williams & Minshew, 2007) used T1 images to parcellate white matter into two components, an "inner" core of sagittal and bridging components (including the corpus callosum) and an "outer" core of radiate white matter. They found (in 6–11-year-old individuals) that the outer radiate white matter (mediating intra-hemispheric connections) was robustly enlarged, whereas the inner core (including the corpus callosum) did not differ significantly from controls (although a majority of studies have found different results in the corpus callosum – see Section 2.3). Similarly, Ben Bashat et al. (2007) performed DTI on 1.8–3.3-year-old individuals with ASD, and reported fractional anisotropy (FA) (a marker of tissue structure that is higher in dense and ordered structure) to be increased relative to controls in radial (but not callosal) white matter, with changes particularly acute in frontal areas. This is suggestive of abnormal early growth of radial white matter structures. (Although this finding appears inconsistent with the Friedman et al. (2006) MRS finding of no histochemical white matter abnormalities in 3–4-year-old subjects with ASD relative to a delayed development group – see Section 3.4.)

These reports of volumic and structural excesses in radial white matter structures have been interpreted (e.g. Casanova et al., 2006a) as suggesting an excess of white matter that mediates local, intra-hemispheric connectivity. A number of other studies, though, have presented findings that appear inconsistent with this model.

As Ben Bashat et al. (2007) point out, their finding of *increased* fractional anisotropy (FA) in 1.8–3.3-year-old subjects stands in sharp contrast to findings elsewhere of *decreased* FA in adolescents and adults with ASD, suggestive of disordered structure. Reduced FA in older age groups has been reported in a range of white matter structures (ventromedial pre-frontal cortex, anterior cingulate gyri and temporo-parietal junction – Barnea-Goraly et al., 2004; superior temporal gyrus and temporal stem – Lee et al., 2007; orbitofrontal cortex, pre-frontal and anterior cingulate – Pardini et al., 2009; bilateral temporal and frontal structures – Cheung et al., 2009), with a recent study that combined DTI with VBM on 6–11-year-old children reporting a mixture of increased and decreased white matter densities in different parts of the brain (Ke et al., 2009; see also Conturo et al., 2008 for similarly mixed results).

Strikingly, Sundaram et al. (2008) recently performed DTI and tractography on frontal lobe white matter on a 2.5–7.5-year-old ASD sample, and reported findings apparently at odds with the local over-connectivity model outlined above. Firstly, they found no difference in average fiber length between their ASD sample and TDs, suggesting no bias in favor of local over long-distance connectivity. Secondly, they report that the total number of intra-frontal fibers was not (as over-connectivity theory would surely predict) greater in the ASD group than the TD controls. (Although they also report the average length of long fibers to be higher in the ASD group, a fact that appears irreconcilable with the previous two findings.)

Other recent work further complicates the picture. A model of local over-connectivity would surely predict shorter fiber length, increased fiber volume and higher fiber density within particular intra-hemispheric white matter tracts; yet Kumar et al. (2009) (who also used DTI and tractography) found results that were much more mixed. For example, within the uncinate fasciculus (UF) (a tract linking the gyri of the frontal lobe with the anterior end of the temporal lobe), they found shorter average fiber length in the left UF but longer average fiber length in the right UF, that was accompanied by increased fiber volume and higher fiber density. Similar results were found in other areas.

In conclusion, whereas some work in this area has pointed to excessive early development of intra-hemispheric white matter (suggestive of excessive intra-hemispheric connectivity), the picture has become considerably more complicated in recent years. Further empirical work (particularly using DTI and tractography) is clearly needed here to resolve these inconsistencies; structural connectivity imaging (particularly using tractography) remains a field in its infancy. Longitudinal studies will be particularly important here; it is disappointing that some authors (e.g. Sundaram et al., 2008) group all 2.5–7.5-year-old subjects into one group, thus possibly obscuring important developmental trends.

3.4. Evidence from post mortem histological analyses

Hutsler and Zhang (2010) performed *post mortem* histological analyses on 10 subjects (aged 10–44) with ASD, along with a similar number of age-matched controls. They found increased dendritic spine densities in subjects with ASD across a number of different dendrite types, in samples taken from different cortical layers (II, III and V) and cortical regions (frontal (BA9), temporal (BA 21) and parietal (BA7). Two aspects of their findings were particularly striking – firstly, that differences were most marked in the most superficial layer II, the relatively late maturing layer that establishes synaptic connections during the postnatal period. Pyramidal cells in layer II are predominantly involved in mediating interconnectivity between cortical regions within a hemisphere (Hutsler & Zhang, 2010). Secondly, that differences in deeper layers (layer V) were also found only in temporal areas, and not in parietal or frontal regions. It should also be noted, though, that these findings were not found across all subjects with ASD – on an age-matched pairwise comparison, only seven of ten subjects showed increased spine densities, and one of those seven was marginal.

Casanova et al. (2006a, 2006b; see also Buxhoeveden et al., 2006; Casanova, Buxhoeveden, Switala, & Roy, 2002) reported data from six post mortem subjects (aged 4–24 – age-related differences are not reported) suggesting mini-columnar structures to be more numerous, more densely packed and smaller in individuals with ASD (although the number of cells per minicolumn appears normal). Because whole brain structural connectivity analyses have consistently shown that a relatively higher proportion of intra-cortical connections are local (Braitenberg, 2001; Sporns & Zwi, 2004), several authors have pointed out (Belmonte et al., 2004; Casanova, Herbert, & Ziegler, 2004; Courchesne & Pierce, 2005a; Courchesne et al., 2007) that increasing the number of neurons within a given area will also lead to a relatively greater increase in the number of local intra-cortical (short-distance) axons relative to distant neural populations (Courchesne et al., 2007).

Hutsler and Zhang (2010), following an idea excellently developed by Courchesne et al. (2007), suggest that alterations in spine densities could be the result of improper synaptic culling during the postnatal period. Research in other fields, though, has provided data that appears inconsistent with this idea, including several recent studies have used magnetic resonance spectroscopy

(MRS), an MRI-derived technique that provides *in vivo* data on tissue-based chemistry and certain cellular features (see Dager, Friedman, Petropoulos, & Shaw, 2008). Friedman et al. (2003) hypothesized that, in conjunction with findings of cerebral enlargement, that children with ASD would exhibit *elevated* N-acetylaspartate (NAA) levels and *reduced* transverse relaxation times for Cho, indicative of an over-proliferation of cells or a reduction in normal pruning. Instead, they found the opposite: in 3–4-year-old children with ASD, they reported *prolonged* gray matter Cho transverse relaxation and (trend-level) *decreased* NAA relative to a delayed development group (Friedman et al., 2006). Similar findings (also implicating Choline-containing compounds, creatine plus phosphocreatine and myo-inositol) have been reported in different brain areas in a range of age groups (e.g. Hisaoka, Harada, Nishitani, & Mori, 2001; Levitt et al., 2003), although inconsistencies remain (see Table 3 in Vasconcelos et al., 2008 for an excellent recent summary).

The exact significance of their findings remains extremely hard to interpret: changes in Cho transverse relaxation, for example, have been variously attributed to chemical maturation of the myelin sheath, displacement of free water in the extracellular space because of increases in axonal diameter, increased dendritic arborization and the development of glial cells (Barkovich, 2005; Dager et al., 2008), a range of factors that would have widely differing computational consequences (see Casanova et al., 2006a; Courchesne et al., 2007; Dager et al., 2008; Friedman et al., 2006; Kleinhans et al., 2008; McCaffery & Deutsch, 2005; Zhang & Sejnowski, 2000).

3.5. Conclusion

There is some, albeit relatively limited, evidence of functional over-connectivity within local networks from fMRI (3.1) and EEG (3.2). From structural MRI and DTI (3.3) the evidence is considerably more mixed – for example, one recent DTI/tractography study reported *shorter* than expected fiber lengths in the left hemisphere and *longer* average fiber lengths in the same area of the right hemisphere (Kumar et al., 2009). It is intriguing that the study with the youngest subjects (1.8–3.3-year-old – Ben Bashat et al., 2007) found *increased* FA in radial (but not callosal) white matter (FA tends to be higher in denser and more ordered tissue), whereas other DTI studies with older subjects have found *decreased* FA in similar areas. It should, though, be noted that interpreting these findings is hard since a huge number of factors affect FA values (Behrens et al., 2003; Conturo et al., 1999; Karlsgodt et al., 2008).

The most convincing evidence in favor of over-connectivity currently comes at the micro level (3.4), revealed through *post mortem* histological analyses. It is important to remember the gulf in spatial scale between histological and neuroimaging work, with hundreds of thousands of neurons contained within a single voxel. This means that evidence found at the histological level might not necessarily manifest in neuroimaging data.

4. Hypothesis 3: connectivity disruptions are uniform across the whole brain in ASD

Early formulations of the theory tended to discuss brain over- and under-connectivity as a whole brain phenomenon. Unsurprisingly, as more evidence has accumulated, this picture has become more detailed. The hypothesis that connectivity disruptions in ASD are uniform across the whole brain can be conclusively rejected; in the following two sections we will discuss what seem to be the most important between-region trends.

4.1. Early vs later-developing cortical areas

Converging evidence suggests the frontal and temporal lobes as the cortical areas most heavily affected in ASD. Post mortem studies (Buxhoeveden et al., 2006; Casanova et al., 2006a, 2006b) have reported minicolumnar disruptions to be particularly acute in frontal areas, with no disruption in samples from the primary visual cortex. Structural MRI studies have reported that overgrowth in autistic 2–4-year-olds implicates the frontal and temporal lobes as sites of peak overgrowth, with parietal and occipital areas relatively less affected (see Courchesne et al., 2007 for a review). DTI studies have reported disruptions to white matter structure in 1.8–3.3-year-old individuals to be particularly acute in frontal areas (Ben Bashat et al., 2007). Functional disconnection of frontal areas has been reported in ASD using fcMRI on executive function (Just et al., 2007; Koshino et al., 2008), language (Kana et al., 2007) and visuomotor tasks (Turner, Frost, Linsenbardt, Mcllroy, & Mueller, 2006; Villalobos et al., 2005) as well as in a resting state (Cherkassky et al., 2006) (see also Courchesne & Pierce 2005b). (In contrast to other studies (e.g. Koshino et al., 2008; Villalobos et al., 2005; see also Magnée, Oranje, van Engeland, Kahn, & Kemner, 2009) that have reported functional connectivity *within* posterior areas to be normal, although frontal-posterior connections *do* seem to be impaired (Just et al., 2007; Koshino et al., 2008; Villalobos et al., 2005). EEG coherence studies have reported theta range local over-connectivity to be particularly acute in frontal and temporal cortices (Murias et al., 2007). Voxel-based morphometry has shown that changes in gray matter volume were associated with better communication skills in numerous frontal regions (Parks et al., 2009). And finally, a number of conventional fMRI studies have shown task performance to be associated with abnormal (Gilbert, Bird, Brindley, Frith, & Burgess, 2008; Kana et al., 2007; Luna et al., 2002; Schmitz et al., 2006) patterns of frontal activity.

Courchesne and Pierce (2005a; see also Courchesne, Redcay, Morgan, & Kennedy, 2005) argue that the explanation for this may be developmental, in that lower-order somatosensory and visual cortices tend to mature before the higher-order association cortices (Bunge & Wright, 2007; Casey, Tottenham, Liston, & Durston, 2005; Gilmore et al., 2007; Gogtay et al., 2004; Huttenlocher, 2002). Pyramidal cell dendritic arbors in frontal gyri, for example, are only 3% of full mature size at birth and 48% of mature size by 2-years-old, whereas in the primary visual cortex they are 33% of full size at birth, and by 2 years they have reached mature size (Gogtay et al., 2004; Huttenlocher, 2002). Compared to more posterior cortices, the frontal cortex undergoes synapse formation later, and for a longer period of time, and develops pyramidal neurons with more synapses and far larger dendritic and axonal arbors (Courchesne & Pierce, 2005a; Huttenlocher, 2002; see also Gogtay et al., 2004; Shaw et al., 2008).

Thus, the pattern of impairment in ASD is consistent with that of early, relatively intact development becoming progressively more disrupted over the first few years of life (Courchesne & Pierce, 2005a; Courchesne et al., 2005). This finding is also consistent with the literature on brain overgrowth, which shows brain sizes in autism to be slightly reduced at birth, dramatically increasing with the first 2 years of life in some but not in all cases (Lainhart, 2006; Redcay & Courchesne, 2005).

4.2. Cortico-subcortical

A number of recent studies have used fMRI (Mizuno et al., 2006; Welchew et al., 2005) and structural MRI (Boucher et al., 2005; McAlonan et al., 2005) to point to a finding that contradicts the global trend towards decreased long-range connectivity: this is that, in some cases, long-distance cortico-subcortical connectivity is

greater than expected relative to controls (for related discussions see Grossberg & Seidman, 2006; Müller, 2008). For example, Mizuno et al. (2006) reported that long-distance thalamo-cortical functional connectivity is actually *increased*, although they also reported an overall tendency towards more diffuse thalamo-cortical correlations. Similar findings have been reported using structural MRI. For example, Boucher et al. (2005) examined correlations between the relative sizes of different brain areas in mature autistic individuals; against a background of weaker between-region volumic correlations they reported stronger correlations between the amygdala and two orbitofrontal areas and between the hippocampus and four frontal areas (see also McAlonan et al., 2005). However, this trend is not reflected in some of the other functional connectivity literature: using fMRI, Kana et al. (2007) reported lower functional correlations between the cingulate gyrus and other areas involved in response inhibition, and Kleinhans et al. (2008) reported reduced functional connectivity to the left amygdala, posterior cingulate and thalamus on a face processing task.

In their discussion, Mizuno et al. (2006) offer an ingenious developmental explanation for their finding: since thalamo-cortical axons develop early compared to long-distance cortico-cortical connections which develop later (Sur & Leamey, 2001), and since looped cortico-thalamo-cortical pathways serve as indirect cortico-cortical connections (Guillery & Sherman, 2002), they suggest that an early strength in thalamo-cortical connections relative to abnormally weak long-distance cortico-cortical connections could lead to an increased reliance on looped cortico-thalamo-cortical pathways.

5. Outstanding questions

5.1. Is disrupted connectivity part of the primary pathogenesis in ASD?

Despite considerable evidence that connectivity *is* disrupted in ASD, controversy persists over what place disrupted connectivity should take within our understanding of the disease. Are connectivity problems best seen as "central", "core" or "primary" in ASD, or are they one of numerous "downstream" features of disrupted system performance? There is some ambiguity in the literature concerning this issue. In their influential formulation of the theory, for example, Just et al. (2004) argue that "autism is a cognitive and neurobiological disorder *marked and caused by* underfunctioning integrative circuitry that results in a deficit of integration of information at the neural and cognitive levels" (italics added). Elsewhere in the same paper, though, they write that "the proximal biological cause(s) of the altered levels of brain activation and functional under-connectivity could be either in gray or white matter or both," and that there could be a number of abnormalities all of which "may arise together, and there is no current consensus on which if any of them is central or causal."

Attempts to answer this question have been frustrated by the considerable difficulties involved in studying early development in ASD, before a diagnosis has been made. Subjects tend to present with a host of already developed symptoms, making causal pathways hard to untangle.

Abnormal development of white matter tracts has been reported using DTI and structural MRI in subjects as young as two years old (Ben Bashat et al., 2007; Hazlett et al., 2005). But does this mean that disruption to white matter tracts comes first? Not necessarily: Hazlett et al. (2005) reported enlargement of both gray and white matter cerebral structures at two years of age, and an MRS study found differences in gray- but not in white-matter chemistry in 3–4-year-olds subjects with ASD (Friedman et al., 2006). This has led other authors (Williams & Minshew, 2007) to argue that the limited data available suggests the opposite conclusion: that gray matter changes may in fact be primary to white matter changes.

Concerning the primacy of disrupted connectivity in ASD, another obstinate factor to be taken into account is that not *all* subjects with ASD appear to have disrupted connectivity. Hutsler and Zhang (2010) found increased dendritic spine density in only a subgroup of 7 out of 10 subjects, with only negligible differences in one of those seven. Alexander et al. (2007), who reported structural disruption to the corpus callosum, identified a significant between-group effect that was attributable to a 35% subgroup of individuals with ASD with significant corpus callosal disruption, with no difference (not even trend) in the remaining 65% of individuals with ASD. Other recent studies have reported similar trends (e.g. only 4 from 7 subjects had frontal white matter abnormalities in Ben Bashat et al., 2007). The tendency of many papers to report only group means is regrettable, since it obscures vital information about within-group heterogeneity.

5.2. To what extent do connectivity disruptions emerge over time?

Another, related factor that remains poorly understood is the degree to which connectivity disruptions might emerge as a *result* of aberrant neural development over time. It is, by now, widely accepted that neural development is a dynamically interactive process (Johnson, 2005; Karmiloff-Smith, 1992; Quartz & Sejnowski, 1997), in which any systemic disruption has widespread consequences (see the excellent discussion of this in Just et al. (2004)). The effect of the environment on the development of connectivity is only beginning to be understood – Keller and Just (2009), for example, showed that teaching reading to poor readers had a significant effect on the FA in the left anterior centrum semiovale after just 100 h of tuition.

One striking factor here is that a number of studies looking at typically developing connectivity (e.g. Fair et al., 2009; Gao et al., 2009; Kelly et al., 2009; Supekar, Musen, & Menon, 2009) have all characterized the development of large-scale brain networks as one of weakening over time of short-range functional connectivity and strengthening over time of long-range functional connectivity. Supekar et al. (2009) argue that, during development, "the dynamic process of over-connectivity followed by pruning, which requires connectivity at the neuronal level, also operates at the systems level, helping to reconfigure and rebalance subcortical and paralimbic connectivity in the developing brain" (cf Johnson, 2005). Seen in this light, the findings of increased short-range functional connectivity and decreased long-range functional connectivity in ASD, along with smaller and less synchronized network activation (e.g. Koshino et al., 2008) may perhaps be seen as a failure to go through a normal developmental process.

On this subject, it is also instructive to note that patterns of local over-connectivity and long-distance under-connectivity have also been reported in other disorders. Fingelkurts et al. (2006) measured EEG coherence in opioid-dependent patients, and reported increased local functional connectivity and decreased long-distance connectivity; Miskovic, Schmidt, Boyle, and Saigal (2009) reported increased local EEG coherence in extremely low birth weight adults. Wang et al. (2009) used fMRI to measure resting state correlations between 90 cortical and subcortical regions in children with ADHD, and reported increased local coherences, together with a decreased tendency towards long-range coherences. This suggests that the pattern of local over- and long-distance under-connectivity reported in ASD may be common across a number of disorders, and may (to a degree) be best understood as resulting from the break-down of normal developmental processes. However, systematic comparisons between disorder groups and across developmental time are clearly needed to assess these possibilities.

5.3. How do the connectivity disruptions in ASD relate to those being reported in other disorders?

Although systematic comparisons are lacking, it is interesting to note that there may be further commonalities between the patterns of disrupted connectivity found in autism and those found in other disorders. For example, "frontal under-connectivity" or "frontal disconnection" (a term coined by Geschwind & Levitt, 2007) has been variously reported using working memory tasks in subjects with schizophrenia (Pachou et al., 2008; see also Friston & Frith, 1995), attention switching tasks in stressed patients (Liston, McEwen, & Casey, 2009), in a resting state in subjects with ADHD (Clarke et al., 2008), and so on (see also depression (Anand et al., 2005), dyslexia (Richards & Berninger, 2008), HIV/AIDS (Melrose, Tinaz, Castelo, Courtney, & Stern, 2008) and aging (Andrews-Hanna et al., 2007)). Another striking commonality is structural disruption to the corpus callosum: as well as in ASD (e.g. Just et al., 2007), this has been reported in dyslexia (von Plessen et al., 2002), developmental language disorder (Preis, Steinmetz, Knorr, & Jäncke, 2000), Tourette's syndrome (Plessen et al., 2004), Down's syndrome (Teipel et al., 2003), Williams syndrome (Tomaiuolo et al., 2002), depression (Lacerda et al., 2005), schizophrenia (Narr et al., 2002), and HIV/AIDS (Thompson et al., 2006). The overlap between how connectivity is disrupted in ASD and in other disorders remains poorly understood.

It should be remembered, though, that the specific factors thought to be driving disrupted connectivity in ASD – most particularly brain overgrowth and increased dendritic spine densities – are *not* factors that are also disrupted in other conditions. In fact, *decreased* spine density has been reported in many developmental disorders, such as fetal alcohol syndrome (Ferrer & Galofre, 1987), severe infant protein-calorie malnutrition (Benitez-Bribiesca, De la Rosa-Alvarez, & Mansilla-Olivares, 1999), infant brain damage (Dietzmann & von Bossanyi, 1994), and Down syndrome (Suetsugu & Mehraein, 1980). Only a few conditions associated with mental retardation have shown an increase in spine densities, including fragile X syndrome (Irwin, Galvez, & Greenough, 2000) and hemimegalencephaly (Takashima, Chan, Becker, & Kuruta, 1991). Similarly, whereas sexual dimorphism in brain growth rates *has* been reported (Gilmore et al., 2007; Baron-Cohen, Knickmeyer, & Belmonte, 2005), reports of group differences in brain growth rates are not (to our knowledge) found in other conditions.

6. Conclusion

We have reviewed (Section 2) fMRI and EEG studies that provide overwhelming evidence of functional under-connectivity within medium- and long-range networks in mature subjects with ASD. We have also reviewed DTI studies that demonstrate inter-hemispheric structural under-connectivity in mature subjects with ASD. With regard to younger subjects, however, there are fewer studies and the evidence is considerably more mixed. In particular, the small number of DTI studies that have used younger (<4-year-old) subjects have produced results that might be at odds with the long-range under-connectivity reported in mature subjects.

A smaller volume of fMRI and EEG work has produced evidence of functional over-connectivity (Section 3), but findings from recent DTI and tractography work are considerably more mixed. We have argued that perhaps the strongest evidence in favor of local over-connectivity comes at the micro- level, from a small number of post mortem histological analyses.

We have discussed some non-uniformities in this picture, for example in reports of over-connectivity within medium-range thalamo-cortical networks (Section 4.2). We have also discussed convergent evidence suggesting that disruptions to and from frontal and temporal cortices may be most heavily disrupted in ASD (Section 4.1). Following others, we suggest that this is consistent with the idea of early, relatively intact development becoming progressively more disrupted during the first few years of life (see also Hazlett et al., 2005; Herbert et al., 2004; Pardo & Eberhart, 2007; Redcay & Courchesne, 2005).

Finally, we have pointed (Section 5) to tantalizing evidence that the increased short-range connectivity and decreased long-range connectivity reported in ASD may resemble that found in immature vs mature typically developing subjects and in subjects with other disorders, which opens the possibility that at least some of the connectivity disruptions seen in autism may best be understood as resulting from a failure to undergo a normal developmental process (e.g. Johnson, 2005).

We have also pointed out that a number of other conditions also feature disrupted frontal connectivity and structural disruption to the corpus callosum, which may question the primacy of these abnormalities in disease models of autism. However, we have noted that the (small-sample) histological work available does appear to suggest micro-structural differences between ASD and other disorders, and that, whereas sexual dimorphism in brain growth rates has been reported, group differences in brain growth rates are not (to our knowledge) found in other conditions. More longitudinal and between-disorder comparisons are clearly need here (see e.g. Greicius, 2008).

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