Published in final edited form as:

Ann N Y Acad Sci. 2008 December ; 1145: 300–315. doi:10.1196/annals.1416.014.

FROM LOCI TO NETWORKS AND BACK AGAIN: ANOMALIES IN THE STUDY OF AUTISM

Ralph-Axel Müller

Brain Development Imaging Laboratory, Department of Psychology, San Diego State University, San Diego, CA 92120; Department of Cognitive Science, University of California, San Diego, CA 92093

Abstract

Recent developments in functional imaging as well as the emergence of new anatomical imaging techniques suited for the study of white matter have shifted investigational paradigms from a localized to a more holistic, network approach. Aside from providing physiological information, functional MRI can be applied to the study of connectivity. However, the concept of “functional connectivity” remains broad, and specific designs and analyses may affect the results. In addition, connectivity cannot be viewed in isolation. Rather, from a developmental perspective, connectivity and local cortical architecture are intimately related. Therefore, combined approaches examining local organization and connectivity are the most promising avenues for elucidating disturbances of neurofunctional organization in developmental disorders. Here this paradigm shift is illustrated via data obtained from autism research, wherein partially converging evidence suggests reduced long-range connectivity between cerebral regions.

Keywords

Localization; functional connectivity; developmental disorders; autism

INTRODUCTION

From loci to networks

In his *Structure of Scientific Revolutions*, Thomas Kuhn (1962) describes how the progress of a science may be characterized by ‘paradigm shifts.’ In his view, a field of research would be dominated by a fixed set of assumptions about an object of study or a set of questions for potentially long periods of time until ‘anomalies,’ i.e., findings that cannot be reconciled with these assumptions, reach a critical threshold. At this point, the field may undergo a sudden ‘revolution’ or ‘paradigm shift,’ resulting in a completely new approach with a new set of fixed assumptions.

In the history of neuropsychology, events have not been as dramatic. One could indeed make the point that the conflict between localizing and holistic approaches to the study of brain function has had a long history through the centuries (Clarke & Dewhurst, 1972). Nonetheless, localizing approaches have been overall dominant, at least since the times of Paul Broca. The reasons are largely methodological. The dominant and most productive techniques of neuropsychology have been ones that naturally lent themselves to conclusions

about localized function. Thus Broca's description (Broca, 1861) of expressive speech loss in patient Leborgne found to be associated with what was then considered as a localized lesion in left inferior frontal cortex was among the first of thousands of cases in which presumably localized lesions in a patient or a group of patients was related to a circumscribed pattern of cognitive or behavioral deficit (see Shallice, 1988 for a methodological review). It is of note that a later re-examination of Leborgne's brain by Signoret et al. (1984) showed much more extensive damage.

In the history of neuropsychology, voices of caution – from Hughlings-Jackson (1878) to Henry Head (1926) or Jason Brown (1988) – have been mostly met with puzzled respect. Certainly, anyone with a basic knowledge of the brain could tell just by appreciating the vast volumes of connecting white matter – that the cooperation of regions in large networks was highly likely. However, incorporating lesion data into holistic or distributed models was less than straightforward, whereas localizing models could generate clear and falsifiable hypotheses – often considered the hallmark of true science (Popper, 1965).

The more recent history of functional neuroimaging has been characterized by a similar methodological bias. The two most important techniques for activation mapping, [^{15}O]-water positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) detect signals based on increased blood flow and blood oxygenation in regions of enhanced synaptic transmission. The signal arises almost exclusively from gray matter. Indeed, effects in white matter are often discarded as artifactual by definition. Although these techniques have almost unlimited ability to detect multiple concurrent activation sites, the function of white matter remains literally in the dark. Not surprisingly, the localizationist program, though much more refined than in the times of the phrenologists (Gall & Spurzheim, 1810) or classical localizationists (Lichtheim, 1885; Wernicke, 1874), has progressed greatly since the emergence of functional neuroimaging. An impressive example is the review by Cabeza and Nyberg (2000) of 275 PET and fMRI studies in which they identify loci of activation sorted by Brodmann areas for a large number of cognitive domains and types of tasks. At the end of this tour de force, Cabeza and Nyberg emphasize that network approaches, although not included in the review, are supported by the finding that any type of task performance appears to rely on multiple brain regions.

This insight may imply that the massive attempt of localizing components of cognitive and sensorimotor function in many thousands of current functional imaging studies of the healthy adult brain has been leading to its own demise, reminiscent of what Kuhn described as a paradigm shift. The added driving forces in this process are the methodological advances in neuroimaging technology. Among these are noninvasive methods of studying white matter integrity (in MR spectroscopy [MRS] and diffusion tensor imaging [DTI]) and fiber tracts (in DTI tractography) on the anatomical side and functional connectivity MRI (fcMRI) on the functional side.

In this review, I will examine how the change in perspective described above – from local specialization to distributed network organization – affects the study of developmental disorders. The exemplary disorder to be discussed will be autism, but many of the issues raised will likely apply to other disorders, such as developmental dyslexia.

“FUNCTIONAL CONNECTIVITY”

One of the pioneers of the study of functional connectivity in developmental disorders, Barry Horwitz, who in the late 1980s was the first to study regional cross-correlations of PET data of glucose metabolism in autism (Horwitz et al., 1988), entitled a recent review (Horwitz, 2003) “The elusive concept of brain connectivity.” While our concept of anatomical connectivity may be straightforward, relating to axons and the tissue

compartments containing them (white matter), the definition of functional connectivity is much less clear. In electrophysiological studies, phase coherence has been applied as a measure of functional connectivity and its changes in childhood have been described (Thatcher et al., 1987). Animal studies, in which electrical currents were recorded directly from the cortex, suggest that phase-locked synchronization of spiking in distal neurons may reflect perceptual binding (Nase et al., 2003). Temporal coherence is found in high frequency domains, in particular in the beta (15–30Hz) and gamma bands (30–80Hz, Uhlhaas & Singer, 2006). Electrophysiological approaches to functional connectivity have been applied to autism in only a few studies. Grice and colleagues (2001) reported reduced modulation of gamma band activity associated with face orientation (upright and inverted) in autistic adults. One additional study by Brown and colleagues (2005) found atypical gamma peaks in autistic adolescents during viewing of illusory shapes, which the authors interpreted as reduced signal-to-noise ratio due to impaired inhibition. Wilson et al. (2006) recently reported reduced gamma band power of magnetoencephalographic responses to acoustic stimuli in the left hemisphere of 10 children with autism whereas gamma power in the right hemisphere was close to normal.

While EEG coherence studies of functional connectivity in autism are still very scarce, some recent studies have applied functional connectivity MRI (fcMRI), which is characterized by lower temporal but higher spatial resolution. Analogous to conventional fMRI, fcMRI is based on the blood oxygenation level dependent (BOLD) signal, which indirectly reflects local neuronal activity (Logothetis & Pfeuffer, 2004). Instead of modeling the variance of BOLD time series in terms of task on-off blocks or trial sequences as in conventional fMRI activation analysis, fcMRI measures interregional cross-correlations of the BOLD signal. Yet, as pointed out in the review by Horwitz (2003), there is no general consensus on what *functional connectivity* exactly means. The term has been defined by Friston (1993) as “observed temporal correlations between spatially remote neurophysiological events” – in contrast with *effective connectivity*, defined as “the influence one neural system exerts over another.” However, this dichotomy is clearer conceptually than it may be in actual research applications. Of course, there is a difference between studies exploring time series correlations without making assumptions about underlying anatomical connectivity and those that model correlations only between selected regions assumed to affect each other through anatomical connectivity as known from animal studies. The distinction is not unlike the two different approaches in statistical activation analyses of fMRI or [¹⁵O]-water PET data, which can be tested either on a voxel-wise basis throughout the brain or with regard to predetermined regions of interest (ROIs, each containing many voxels). However, no one would assume that functional connectivity, as originally defined by Friston or more recently by Rippon and colleagues (2006) as a “temporal relationship between two or more neuronal assemblies acting synchronously, measured by cross-correlating time series,” could exist in the absence of effective connectivity and anatomical connections.

In actual research practice, the lines between functional and effective connectivity are often not as distinct. For example, Castelli and colleagues (2002) reported reduced activation associated with a ‘theory of mind’ condition (e.g., observing triangles that appeared to interact like human beings) in superior temporal sulcus (STS), basal temporal cortex (close to the amygdala), and medial prefrontal cortex of the right hemisphere in adults with autism spectrum disorders (ASD). Their connectivity analysis focused on these regions, which were activated by the control group, and extrastriate cortex, which was activated by both groups. They found connectivity between extrastriate cortex and STS was reduced in the autism group. Since connectivity analyses were limited to ROIs, they may be considered as related to effective connectivity. Although the authors did not explicitly establish the existence of anatomical connectivity between the ROIs, the assumption is almost trivial in view of the density and abundance of anatomical connectivity in the brain (Schmahmann & Pandya,

2006). This is particularly so, because the low temporal resolution of PET and fMRI does not warrant any assumption about observed connectivity being monosynaptic. The ease with which anatomical connections, through which brain regions may affect each other functionally, can be established for just about any interregional functional signal correlation thus softens the dichotomy between functional and effective connectivity. The dichotomy appears to be more related to the investigator's approach than to an actual biological distinction.

There is an important additional issue already alluded to in the previous example, in which ROIs were selected on the basis of activation findings. Many variants of connectivity studies consider functional or effective connectivity a derivation of task-driven activation effects. For example, dynamic causal modeling includes effects of experimental conditions on connectivity (Lee et al., 2006). This stands in contrast to the evidence that first jumpstarted fMRI. Biswal and colleagues (1995) identified primary motor cortex using a simple finger movement paradigm. Using the observed activation cluster in left motor cortex as a seed volume, they demonstrated BOLD time series cross-correlations specifically in other brain regions considered part of a motor network (e.g., homotopic contralateral primary motor cortex and supplementary motor areas). Remarkably, these correlations were seen during rest, i.e., in the absence of any task or stimulation. Furthermore, such correlations have been predominantly observed at very low frequencies below 0.1Hz (Cordes et al., 2001). This suggests that there are components in the BOLD time series that reflect neural network organization and that are not driven by stimulation or cognitive challenge. There are two implications, one promising, the other problematic. First, low-frequency BOLD correlations promise to open a window onto functional brain organization that may be orthogonal to conventional activation imaging, providing an entirely independent set of useful evidence. Second, however, since these low-frequency correlations cannot be explained by hemodynamic responses to task challenge, it is not clear what their functional and neurophysiological basis is. There is some evidence suggesting that these fMRI effects may reflect low-frequency fluctuations in local field potentials, possibly driven by thalamo-cortical afferents (Leopold et al., 2003).

Despite the lack of a comprehensive physiological model, there are growing numbers of studies supporting the validity of low frequency BOLD correlations for mapping out functionally specialized networks. These include, for example, studies mapping out complex distributed functional networks, such as the motor network (Xiong et al., 1999), perisylvian language areas (Hampson et al., 2002), or regions cooperating on a spatial working memory task (Lowe et al., 2000) as well as some intriguing clinical studies. One study in patients with callosal agenesis showed disrupted interhemispheric BOLD correlations between homotopic regions, such as left and right superior temporal cortex, which are robustly correlated in healthy controls (Quigley et al., 2003). Another study reported that a polymorphism of the serotonin transporter gene implicated in anxiety disorders and depression was associated with changes in BOLD signal correlation between amygdala and perigenual anterior cingulate cortex (Pezawas et al., 2005). fMRI effects between these two regions were also much stronger predictors of harm avoidance scores than BOLD activation or gray matter volume in either of the two regions.

ANATOMICAL EVIDENCE ON CONNECTIVITY IN AUTISM

Before turning to applications of functional connectivity in a developmental disorder such as autism, the question arises why such an endeavor would be reasonable. The very general considerations about a 'paradigm change' in cognitive neuroscience towards network models alone would be a rather slim rationale for investing in such studies of a developmental disorder. However, there are several lines of independent evidence

suggesting that connectivity approaches will indeed be useful in autism research. The first relates to neuroanatomical studies.

Although some reports may have suggested specific and potentially localizing impairments in brain regions such as the posterior cerebellar vermis (Courchesne et al., 1988) or the amygdala (Baron-Cohen et al., 2000), the structural MRI and postmortem literature on autism, not unlike that of developmental dyslexia, is extremely diverse, with findings in many regions, such as frontal (Herbert et al., 2004), temporal (Kwon et al., 2004; Rojas et al., 2005), and parietal lobes (Courchesne et al., 1993), cingulate gyrus (Haznedar et al., 1997), corpus callosum (Vidal et al., 2006), hippocampus and amygdala (Otsuka et al., 1999), thalamus (Tsatsanis et al., 2003), basal ganglia (Hollander et al., 2005), and brainstem (Rodier, 2002). This diversity of findings may be partly attributed to heterogeneity within the population that meets diagnostic criteria and the existence of multiple etiological pathways linking genetic and epigenetic risk with phenotypic impairment (Folstein & Rosen-Sheidley, 2001; Herbert et al., 2006). In addition, however, it likely reflects the truly distributed nature of brain involvement in autism (see Müller, 2007 for review). Support for this distributed view of anatomical impairment comes from studies showing abnormal growth patterns in autism with early postnatal overgrowth followed by reduced growth (Courchesne et al., 2001; Hazlett et al., 2005; Sparks et al., 2002). These growth defects affect both gray and white matter throughout the brain (with the possible exception of the occipital lobe, Carper et al., 2002). Such widely distributed brain growth abnormalities could relate to atypical profiles of brain growth factors that were observed in neonates later diagnosed with autism (Nelson et al., 2006).

It should be noted that some MR volumetric and voxel-based morphometry studies have not yielded significant findings of white matter abnormalities (Hazlett et al., 2005; McAlonan et al., 2005). However, the profile of early overgrowth and subsequently reduced growth, as mentioned above and reviewed in Redcay and Courchesne (2005), may explain such null findings in older autistic children and adults. From this perspective, apparently normal brain volume may not necessarily reflect normally developed and organized fiber tracts, but may be the outcome of a sequence of disturbances with inverse polarity. In addition, some studies examining more specific aspects of white matter have identified abnormalities. One highly replicated finding of reduced white matter volume in autism concerns the corpus callosum (Alexander et al., 2007; Chung et al., 2004; Egaas et al., 1995; Piven et al., 1997; Vidal et al., 2006; Waiter et al., 2005).

Volumetric MRI studies examine white matter solely with regard to size. As mentioned, normal size can conceal qualitative white matter compromise and in turn affect interregional cooperation. One study by Hendry and colleagues (2006) found increased transverse (T2) relaxation times of white matter in parieto-occipital and some prefrontal regions, suggesting abnormally high water content. While most MR spectroscopy (MRS) studies have measured large voxels with partial volume effects (including both gray and white matter), Friedman and coworkers (2006) found that *N*-acetylaspartate (NAA) and *Myo*-inositol, respectively considered to be markers of neuronal and membrane integrity, were reduced in the white matter of autistic children around four years of age. However, a similar reduction was also seen in non-autistic children with developmental delays, suggesting that this finding was not specific to autism. Another MRS study of white matter in slightly older autistic children failed to detect reduced NAA in comparison to typical controls (Fayed & Modrego, 2005).

MRS detects only a limited set of metabolites. Null findings therefore do not confirm white matter integrity. An alternative approach to the study of white matter is provided by diffusion-tensor imaging (DTI), which takes advantage of the effects on magnetic resonance of the movement of water molecules. Since axonal membranes in white matter prevent water

molecules from diffusing freely in all directions (isotropically), fractional anisotropy, which can be measured in DTI, reflects the integrity and organization of axons (Le Bihan, 2003). One DTI study in male autistic adolescents by Barnea-Goraly (2004) found widespread reductions in fractional anisotropy (FA) in a comparison with matched control participants. Some of the effects, which were seen in all four lobes of the cerebrum, were consistent with previous findings from other techniques, such as reductions in anterior portions of the corpus callosum and in ventromedial prefrontal cortex. Other sites of reduced FA in occipital and pericentral regions were less expected. In a more recent DTI study, Alexander and colleagues (2007) reported reduced volume and fractional anisotropy accompanied by increased diffusivity in the corpus callosum, suggesting white matter compromise affecting interhemispheric connections in children and adults with autism. Keller and colleagues (2007) found several small foci of significantly reduced FA in or close to the callosum and in the corona radiata in children and adults with autism. In most of these sites, reductions in FA were age-independent and persisted into mid-adulthood.

The findings reviewed above indicate that although white matter volume may be in the normal range in many individuals with autism (with the possible exception of children under the age of 5 years), several MR modalities that examine organization and integrity, rather than volume alone, point at significant compromise. It is therefore reasonable to expect functional reflections of compromised anatomical connectivity in autism. I will now turn to studies examining functional connectivity in autism more directly.

FUNCTIONAL CONNECTIVITY IN AUTISM

The field of fMRI research on developmental disorders remains quite limited. In conclusion from fMRI findings in a study on sentence comprehension in high-functioning autistic adults, Just and colleagues (2004) formulated an 'underconnectivity theory' of autism. They observed that in autistic participants BOLD signal cross-correlations associated with task performance (determining the agent or recipient in a sentence by pressing a button) was slightly reduced (though generally present) between a number of cortical regions of interest. Largely consistent findings have been reported in additional studies by Just and colleagues on verbal working memory (Koshino et al., 2005), semantic judgments of sentences (Kana et al., 2006), and executive processing on the Tower of London task (Just et al., 2006). In some of these studies, interesting correlations between reduced functional connectivity and other measures were found. For example, Just and colleagues (2006) found that functional connectivity associated with their executive task was not only reduced overall in their autism group, but also positively correlated with the size of the callosal genu area and negatively correlated with the total score on the Autism Diagnostic Observation Schedule (ADOS, Lord et al., 2001).

In view of this series of studies, it would be tempting to conclude that the autistic brain is characterized by generalized underconnectivity affecting long-range fibers. However, this conclusion is less obvious when considering the autism literature on functional connectivity in its entirety. In one study, which included 13 adult autism spectrum disorder (ASD) participants, Welchew and colleagues (2005) examined Pearson correlation matrices for 90 cortical and subcortical ROIs. While they observed reduced connectivity for the amygdala and parahippocampal gyrus (in their comparison with matched controls), no evidence of generalized underconnectivity was seen. In fact, many ROI pairings showed greater functional connectivity in their autism sample compared to the control group. Furthermore, since participants were scanned while viewing faces with fearful expressions, findings in the medial temporal lobe may have been driven by group differences in activation effects rather than by functional connectivity effects in the strict sense (as discussed previously).

fcMRI results from our own group have also not been consistent with a generalized underconnectivity hypothesis. In one study (Villalobos et al., 2005), functional connectivity of primary visual cortex was examined. Data were acquired during simple conditions of visuomotor coordination, but task effects were minimized through orthogonal regressors (smoothed task-control boxcars). The context of this study was the hypothesis of defects in the mirror neuron system (associated with impaired imitation and action understanding) in autism (Williams et al., 2001). The main focus was therefore on functional connectivity with inferior frontal cortex (one of the presumed sites of mirror neurons (Rizzolatti & Craighero, 2004)), which was indeed significantly reduced bilaterally. However, functional connectivity between V1 and temporal and parietal lobes was not found to be significantly reduced.

Two other fcMRI studies of autism recently examined connectivity between subcortex and cerebral cortex. In the first one (Mizuno et al., 2006), seed volumes were placed in the thalamus because thalamic abnormalities in autism have been observed in a number of studies. These include an early PET study showing reduced correlation of glucose metabolic rates between thalamus and fronto-parietal cortex (Horwitz et al., 1988) to more recent studies demonstrating reduced neuronal integrity in the autistic thalamus (Friedman et al., 2003), reduced thalamic perfusion (Ryu et al., 1999; Starkstein et al., 2000), and reduced thalamic volume (Tsatsanis et al., 2003). Contrary to expectations, however, the fcMRI study by Mizuno et al. (2006) showed partially greater than normal functional connectivity between thalami and cortex, particularly in bilateral pericentral as well as inferior frontal and insular regions. In a second study, Turner and colleagues (2006) examined connectivity between caudate nuclei and cerebral cortex in autism. This study was motivated by structural and metabolic findings indicating abnormalities in the caudate nuclei in autism (Levitt et al., 2003; Sears et al., 1999). Similar to the study on thalamocortical connectivity, we found partial overconnectivity between caudate nuclei and cerebral cortex in autism, again primarily in or close to perirolandic sensorimotor regions.

In summary, while many studies of anatomical and functional connectivity are consistent with a hypothesis of underconnectivity in autism proposed by Just and colleagues (2004), non-replications in several studies are puzzling. One potential explanation relates to the question of activation effects in fcMRI analyses, as discussed earlier. It is possible that interregional correlations found to be reduced in ASD in the studies by Just and colleagues were partly driven by activation effects whereas in the studies showing partially increased functional connectivity, activation effects were minimized by orthogonal task regressors and low-pass temporal filtering. As discussed above, functional connectivity effects were originally detected in the absence of a task and in frequencies below 0.1Hz (Biswal et al., 1995). An alternative – less technical and more biological – interpretation of the current findings might suggest predominant cortico-cortical underconnectivity and predominant subcortico-cortical overconnectivity. Fiber tract anomalies reflected in fcMRI results may relate to recent findings of early developmental abnormalities in white matter growth (Carper et al., 2002).

The findings of atypically increased subcortico-cortical fcMRI effects in the studies by Mizuno and colleagues (2006) and by Turner et al. (2006) should, however, not be considered evidence for “overconnectivity” in any functionally beneficial way. Instead, it is conceivable that these effects reflect atypically diffuse connectivity. Thalamocortical connectivity, for example, is highly organized and functionally segregated in the typical brain, with most thalamic nuclei connecting to specific cortical regions (Sherman & Guillery, 2001). Although the study by Mizuno et al. (2006) did not have sufficient spatial resolution to identify functional connectivity for individual thalamic nuclei, the results may suggest atypically undifferentiated connectivity between thalamus and cerebral cortex in

autism. In the final section, I will therefore now turn to the developmental roots of potential connectivity defects.

DEVELOPMENTAL LINKS BETWEEN CONNECTIVITY AND LOCAL ARCHITECTURE

Early in this review, I referred to ‘anomalies’ in localizing approaches to the neurofunctional organization of the adult brain. Such anomalies are even more prevalent in localizing models of developmental disorders (Thomas & Karmiloff-Smith, 2002). In development, the relevance of connectivity goes beyond the cooperation of brain regions. Connections are established and retracted in response to activity (Kandel et al., 2000). Regions in distal parts of the brain may affect each other’s functional and structural organization through connectivity, e.g., through transfer of activity, as seen in developing thalamocortical connectivity (O’Leary & Nakagawa, 2002; Sur et al., 2002). Connectivity therefore plays a larger role than just allowing a collection of mature and specialized regions to “talk” to each other. Staying with the metaphor, development connectivity may help each region to learn how to “talk intelligibly”.

From a microscopic and cellular point of view, this outcome is completely expected. Connections are axons and thus processes of neurons whose somata and dendrites populate gray matter. The common procedure of tissue segmentation in neuroimaging, separating white matter from gray matter “compartments,” is a useful (though misleading) artifact of technical limitations that prevent us from examining individual cells in the human brain *in vivo*. In reality, white matter is largely constituted by the processes of nerve cell bodies in gray matter. White matter and the connectivity it affords, are thus a correlate of the architecture of gray matter rather than a distinct or “segmentable” tissue compartment. Therefore, any change of perspective in the study of developmental disorders from local specialization to network organization cannot imply that local architecture is irrelevant. It would be foolish to conclude that the search for functional specializations in cytoarchitectonic regions initiated by Korbinian Brodmann at the turn of the 20th century was fruitless and is now to be succeeded by the exclusive study of connectivity.

Developmentally speaking, connectivity and local architecture are outcomes of neuronal migration and differentiation, i.e., two aspects of the same set of events. It is known from animal studies that afferent input can have dramatic effects on the functional differentiation of cortex. For example, Sur and colleagues (1990) ‘rewired’ retinal afferents in newborn ferrets to the medial geniculate nucleus of the thalamus, which in turn connects to primary auditory cortex in the superior temporal lobe. They could show that due to modified thalamic afferent input, ‘auditory’ cortex responded to visual stimuli and indeed became functionally involved in behavioral responses to visual stimuli (von Melchner et al., 2000). While these results – or findings by Schlaggar et al. (1991) suggesting similar changes due to thalamocortical afferents in transplanted occipital cortex – are usually considered evidence of developmental cross-modal plasticity, they highlight the intimate links between connectivity and the differentiation of local functional architecture in cortex. Such principles are harder to demonstrate in the living human brain although studies of cross-modal plasticity in early deaf and early blind people are entirely consistent (Amedi et al., 2004; Finney et al., 2001; Sadato et al., 2002).

What are the implications for the study of developmental disorders such as autism? In the previous section, I laid out some of the evidence of defects in connectivity in ASD. However, these intriguing and important findings should not suggest that we turn away from the study of local architecture and local functional differentiation because the true causes for cognitive impairments in ASD lie solely in connectivity. The evidence from developmental

neuroscience referred to above underscores that local specificity and connectivity are really only two aspects of the same set of developmental processes. Activation mapping by means of PET and fMRI has indeed generated a large number of brain regions with suspected local abnormality, such as the fusiform gyrus (Pierce & Courchesne, 2001; Schultz et al., 2000) or the medial prefrontal cortex (Castelli et al., 2002; Happé et al., 1996). Aside from some non-replications (Hadjikhani et al., 2004; Pierce et al., 2004), such findings do not necessarily indicate locally compromised cortical function, but they may be indicative of experiential effects (as discussed in detail in Müller, 2007; in press). Absence of significant activation effects in a group analysis may also reflect greater variability of activation sites in individuals of a group (e.g., Pierce et al., 2001). Very few autism fMRI studies have presented findings on a single-subject level. In one study we (Müller et al., 2001) found that what appeared to be reduced motor-related activity in a group analysis of an autism sample was in fact explained by atypical scatter of activation effects in several individuals with autism, which contrasted with consistent, rather focal activity in primary motor cortex seen in matched control individuals. However, given the low contrast-to-noise ratio of single subject analyses, it remains hard to determine whether these results truly indicate an interesting aspect of compromised cortical architecture, such as “hierarchical crowding”. The term ‘hierarchical crowding’ is adapted from the concept of crowding (cf. Lidzba et al., 2006), according to which reorganization of language into the right hemisphere in children with early left hemisphere damage results secondarily in lowered visuospatial function because these typical right hemisphere functions are ‘crowded out’ of right hemisphere regions typically crucial for visuospatial cognition. ‘Hierarchical crowding’ in autism refers to the hypothesis that due to early compromise of cortical architecture and reduced processing efficiency, early developing relatively simple sensorimotor functions occupy atypically large cortical territories at the expense of later developing polymodal and executive functions (Müller et al., 2003). In general, the spatial resolution of PET and of common fMRI protocols is too low to identify more microscopic abnormalities of cortical architecture. In the remainder of this section, I will therefore turn to techniques more appropriate for the study of local architecture in autism.

In one *in vivo* study, Hardan and colleagues (2004) used structural MRI data to calculate a gyrification index for the frontal lobes, reflecting cortical folding. The index was significantly increased for the left frontal lobe in children (but not adults) with ASD, which may be consistent with abnormal growth profiles discussed earlier. The results may be developmentally relevant because cortical folding may be considered a result of neuronal migration. Migrational disturbances possibly reflected in increased cortical folding would probably affect the layered architecture of emerging neocortex in the fetal brain.

While such conclusions from *in vivo* findings remain speculative, postmortem studies permit a more direct examination of local cytoarchitecture. However, just as in studies of dyslexia, postmortem studies in autism are limited by small sample sizes, large demographic and clinical variability of deceased subjects, and often by availability of only small parts of the brain to a given group of researchers. Nonetheless, it is clear that abnormalities in cellular organization are quite common in autism although findings may vary individually (see reviews in Bauman & Kemper, 2005; Palmen et al., 2004; Pickett & London, 2005). Among the more consistent findings have been cellular abnormalities in the limbic system, such as reduced neuronal size and increased cell packing density (Bauman & Kemper, 1994; Raymond et al., 1996) or reduced numbers of neurons (Schumann & Amaral, 2006) in the medial temporal lobe (amygdala, hippocampus etc.) and possibly in the anterior cingulate gyrus (Bauman & Kemper, 2005). Relatively consistent has also been the finding of decreased numbers (Bailey et al., 1998; Ritvo et al., 1986) or size (Fatemi et al., 2002; Fehlow et al., 1993) of cerebellar Purkinje cells.

Other cytoarchitecture findings have been less widely replicated. Brainstem abnormalities affecting superior (Rodier et al., 1996) and inferior (Bailey et al., 1998) olives have been noted in a few cases. Bailey and colleagues (1998) also reported various patterns of cortical dysgenesis or neuronal ectopias in six cases, mostly in the frontal lobe. A recent study of cortical layering in autism (Hutsler et al., 2006) also found more frequent cases of supernumerary neurons in layer I (which usually contains no nerve cell bodies in the mature brain) and in the subplate (below layer VI). However, these findings were qualitative whereas no statistically significant differences in cortical thickness and layering were observed between eight autism and eight control brains (ages 14–45 years).

Casanova and colleagues (2002b) reported that cortical minicolumns were smaller, more numerous, and more dispersed in fronto-temporal areas (9, 21, 22) of nine autistic brains (ages 5–28 years). Analogous findings in two cases of Asperger's disorder (ages 22 and 79 years) were also reported (Casanova et al., 2002a). This pattern of minicolumnar abnormalities has been seen in one additional autism case at age three years, throughout frontal cortex and was accompanied by laminar disorganization (cf. Courchesne & Pierce, 2005). It has been argued that minicolumnar abnormalities may be one of the correlates of atypical developmental trajectories of serotonin synthesis (Chandana et al., 2005).

Minicolumns are considered to derive from ontogenetic columns (Buxhoeveden & Casanova, 2002), which in turn reflect the vertical migration of neurons from the ventricular zone into the cortical plate along radial glial cells (Rakic et al., 2004). This would suggest that neuronal migration in the second gestational trimester may be affected in autism. Suspected minicolumnar abnormalities also tie in with another line of evidence implicating thalamocortical connections. As discussed above, there is some evidence for abnormal thalamocortical connectivity in ASD. Additional indirect evidence consistent with thalamocortical compromise in autism includes findings of reduced serotonin synthesis capacity in thalamus and middle frontal gyrus (Chugani et al., 1997) and reduced beta spectral amplitude during REM sleep, considered to reflect atypical thalamocortical connectivity (Daoust et al., 2004).

Potential compromise of thalamocortical connections in autism is relevant because these connections play an important role in regional functional differentiation of developing neocortex. According to Rakic's widely accepted radial unit and protomap hypotheses (Rakic, 1988; Rakic et al., 2004), cortical columns derive from neuronal clones migrating vertically along radial glial cells. Guidance molecules for thalamocortical afferents are expressed by neurons in the subplate according to their progenitors' spatial position in the ventricular zone or "protomap" (O'Leary & Borngasser, 2006). Thalamocortical connections are thus intimately and interactively tied to neocortical functional differentiation. Besides being guided by chemical information in the subplate of developing cortex, it was already discussed above that thalamocortical afferents in turn have substantial impact on the emerging functional specificity of initially pluripotential cortex (O'Leary & Nakagawa, 2002; Schlaggar & O'Leary, 1991; Sur et al., 2002).

Fundamental disturbances of cortical circuitry in autism probably go beyond minicolumnar anomalies described above. For example, Rubenstein and Merzenich (2003) proposed a model of generally increased excitation/inhibition ratio in the autistic brain. Support comes from cognitive findings of autistic impairments that may reflect 'noisy processing,' clinical evidence of increased prevalence of epileptiform EEG, as well as genetic and molecular evidence implicating excitatory (glutamatergic) and inhibitory (GABAergic) systems (as reviewed in Rubenstein & Merzenich, 2003). GABAergic disturbances may in turn be related to serotonergic anomalies that are well documented in autism (Betancur et al., 2002; Chugani, 2004).

CONCLUSIONS

In conclusion, although findings of compromised local architecture and of abnormal connectivity in the autism literature are largely derived from separate lines of research using different methodological approaches, they are likely to reflect two aspects of largely overlapping sets of developmental disturbances. In other developmental disorders, such as dyslexia, the nature and timing of developmental disturbances will differ and so will the patterns of compromise in local architecture and connectivity. However, considerations regarding autism reviewed here will likely apply in similar ways because they are based on general principles of developmental neuroscience, through which locally differentiated architecture and functional specialization are intimately tied to the connectivity and the transfer of activity in emerging networks.

Acknowledgments

Preparation of this review was supported by the National Institutes of Health, grants R01-NS43999 and R01-DC6155.

REFERENCES

- Alexander AL, Lee JE, Lazar M, Boudos R, Dubray MB, Oakes TR, et al. Diffusion tensor imaging of the corpus callosum in Autism. *Neuroimage*. 2007; 34(1):61–73. [PubMed: 17023185]
- Amedi A, Floel A, Knecht S, Zohary E, Cohen LG. Transcranial magnetic stimulation of the occipital pole interferes with verbal processing in blind subjects. *Nat Neurosci*. 2004; 7(11):1266–1270. [PubMed: 15467719]
- Bailey A, Luthert P, Dean A, Harding B, Janota I, Montgomery M, et al. A clinicopathological study of autism. *Brain*. 1998; 121:889–905. [PubMed: 9619192]
- Barnea-Goraly N, Kwon H, Menon V, Eliez S, Lotspeich L, Reiss AL. White matter structure in autism: preliminary evidence from diffusion tensor imaging. *Biol Psychiatry*. 2004; 55(3):323–326. [PubMed: 14744477]
- Baron-Cohen S, Ring HA, Bullmore ET, Wheelwright S, Ashwin C, Williams SC. The amygdala theory of autism. *Neurosci Biobehav Rev*. 2000; 24(3):355–364. [PubMed: 10781695]
- Bauman, ML.; Kemper, TL. Neuroanatomic observations of the brain in autism. In: Bauman, ML.; Kemper, TL., editors. *The Neurobiology of Autism*. Baltimore: Johns Hopkins UP; 1994. p. 119–145.
- Bauman ML, Kemper TL. Neuroanatomic observations of the brain in autism: a review and future directions. *Int J Dev Neurosci*. 2005; 23(2–3):183–187. [PubMed: 15749244]
- Betancur C, Corbex M, Spieleswoy C, Philippe A, Laplanche JL, Launay JM, et al. Serotonin transporter gene polymorphisms and hyperserotonemia in autistic disorder. *Mol Psychiatry*. 2002; 7(1):67–71. [PubMed: 11803447]
- Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn Reson Med*. 1995; 34(4):537–541. [PubMed: 8524021]
- Broca P. Remarques sur le siège de la faculté du langage articulé, suivies d'une observation d'aphémie (perte de la parole). *Bulletins et Mémoires de la Société Anatomique de Paris*. 1861; 36:330–357.
- Brown C, Gruber T, Boucher J, Rippon G, Brock J. Gamma abnormalities during perception of illusory figures in autism. *Cortex*. 2005; 41(3):364–376. [PubMed: 15871601]
- Brown, JW. Introduction: Microgenetic theory. In: Brown, JW., editor. *The Life of the Mind*. Hillsdale (NJ): Lawrence Erlbaum; 1988. p. 1–26.
- Buxhoeveden DP, Casanova MF. The minicolumn hypothesis in neuroscience. *Brain*. 2002; 125(Pt 5): 935–951. [PubMed: 11960884]
- Cabeza R, Nyberg L. Imaging cognition II: an empirical review of 275 PET and fMRI studies. *Journal of Cognitive Neuroscience*. 2000; 12:1–47. [PubMed: 10769304]
- Carper RA, Moses P, Tigue ZD, Courchesne E. Cerebral lobes in autism: early hyperplasia and abnormal age effects. *Neuroimage*. 2002; 16(4):1038–1051. [PubMed: 12202091]

- Casanova MF, Buxhoeveden DP, Switala AE, Roy E. Asperger's syndrome and cortical neuropathology. *J Child Neurol.* 2002a; 17(2):142–145. [PubMed: 11952076]
- Casanova MF, Buxhoeveden DP, Switala AE, Roy E. Minicolumnar pathology in autism. *Neurology.* 2002b; 58(3):428–432. [PubMed: 11839843]
- Castelli F, Frith C, Happe F, Frith U. Autism, Asperger syndrome and brain mechanisms for the attribution of mental states to animated shapes. *Brain.* 2002; 125(Pt 8):1839–1849. [PubMed: 12135974]
- Chandana SR, Behen ME, Juhasz C, Muzik O, Rothermel RD, Mangner TJ, et al. Significance of abnormalities in developmental trajectory and asymmetry of cortical serotonin synthesis in autism. *Int J Dev Neurosci.* 2005; 23(2–3):171–182. [PubMed: 15749243]
- Chugani DC. Serotonin in autism and pediatric epilepsies. *Ment Retard Dev Disabil Res Rev.* 2004; 10(2):112–116. [PubMed: 15362166]
- Chugani DC, Muzik O, Rothermel RD, Behen ME, Chakraborty PK, Mangner TJ, et al. Altered serotonin synthesis in the dentato-thalamo-cortical pathway in autistic boys. *Annals of Neurology.* 1997; 14:666–669. [PubMed: 9382481]
- Chung MK, Dalton KM, Alexander AL, Davidson RJ. Less white matter concentration in autism: 2D voxel-based morphometry. *Neuroimage.* 2004; 23(1):242–251. [PubMed: 15325371]
- Clarke, E.; Dewhurst, K. *An Illustrated History of Brain Function.* Oxford: Sanford; 1972.
- Cordes D, Haughton VM, Arfanakis K, Carew JD, Turski PA, Moritz CH, et al. Frequencies contributing to functional connectivity in the cerebral cortex in "resting-state" data. *AJNR Am J Neuroradiol.* 2001; 22(7):1326–1333. [PubMed: 11498421]
- Courchesne E, Karns CM, Davis HR, Ziccardi R, Carper RA, Tigue ZD, et al. Unusual brain growth patterns in early life in patients with autistic disorder: an MRI study. *Neurology.* 2001; 57(2):245–254. [PubMed: 11468308]
- Courchesne E, Pierce K. Why the frontal cortex in autism might be talking only to itself: local over-connectivity but long-distance disconnection. *Curr Opin Neurobiol.* 2005; 15(2):225–230. [PubMed: 15831407]
- Courchesne E, Press GA, Yeung-Courchesne R. Parietal lobe abnormalities detected with MR in patients with infantile autism. *American Journal of Roentgenology.* 1993; 160(2):387–393. [PubMed: 8424359]
- Courchesne E, Yeung-Courchesne R, Press GA, Hesselink JR, Jernigan TL. Hypoplasia of cerebellar vermal lobules VI and VII in autism. *New England Journal of Medicine.* 1988; 318(21):1349–1354. [PubMed: 3367935]
- Daoust AM, Limoges E, Bolduc C, Mottron L, Godbout R. EEG spectral analysis of wakefulness and REM sleep in high functioning autistic spectrum disorders. *Clin Neurophysiol.* 2004; 115(6):1368–1373. [PubMed: 15134704]
- Egaas B, Courchesne E, Saitoh O. Reduced size of corpus callosum in autism. *Archives of Neurology.* 1995; 52(8):794–801. [PubMed: 7639631]
- Fatemi SH, Halt AR, Realmuto G, Earle J, Kist DA, Thuras P, et al. Purkinje cell size is reduced in cerebellum of patients with autism. *Cell Mol Neurobiol.* 2002; 22(2):171–175. [PubMed: 12363198]
- Fayed N, Modrego PJ. Comparative study of cerebral white matter in autism and attention-deficit/hyperactivity disorder by means of magnetic resonance spectroscopy. *Acad Radiol.* 2005; 12(5):566–569. [PubMed: 15866128]
- Fehlow P, Bernstein K, Tennstedt A, Walther F. Autism infantum und exzessive aerophagie mit symptomatischem megakolon und ileus bei einem fall von ehlers-danlos-syndrom (Infantile autism and excessive aerophagy with symptomatic megacolon and ileus in a case of Ehlers-Danlos syndrome). *Padiatrie und Grenzgebiete.* 1993; 31(4):259–267. [PubMed: 8259320]
- Finney EM, Fine I, Dobkins KR. Visual stimuli activate auditory cortex in the deaf. *Nat Neurosci.* 2001; 4(12):1171–1173. [PubMed: 11704763]
- Folstein SE, Rosen-Sheidley B. Genetics of autism: complex aetiology for a heterogeneous disorder. *Nat Rev Genet.* 2001; 2(12):943–955. [PubMed: 11733747]

- Friedman SD, Shaw DW, Artru AA, Dawson G, Petropoulos H, Dager SR. Gray and white matter brain chemistry in young children with autism. *Arch Gen Psychiatry*. 2006; 63(7):786–794. [PubMed: 16818868]
- Friedman SD, Shaw DW, Artru AA, Richards TL, Gardner J, Dawson G, et al. Regional brain chemical alterations in young children with autism spectrum disorder. *Neurology*. 2003; 60(1): 100–107. [PubMed: 12525726]
- Friston KJ, Frith CD, Frackowiak RSJ. Time-dependent changes in effective connectivity measured with PET. *Human Brain Mapping*. 1993; 1:69–79.
- Gall, FJ.; Spurzheim, K. *Anatomie und Physiologie des Nervensystems im allgemeinen, und des Gehirnes insbesondere*. Paris: Schoell; 1810.
- Grice SJ, Spratling MW, Karmiloff-Smith A, Halit H, Csibra G, de Haan M, et al. Disordered visual processing and oscillatory brain activity in autism and Williams syndrome. *Neuroreport*. 2001; 12(12):2697–2700. [PubMed: 11522950]
- Hadjikhani N, Joseph RM, Snyder J, Chabris CF, Clark J, Steele S, et al. Activation of the fusiform gyrus when individuals with autism spectrum disorder view faces. *Neuroimage*. 2004; 22(3):1141–1150. [PubMed: 15219586]
- Hampson M, Peterson BS, Skudlarski P, Gatenby JC, Gore JC. Detection of functional connectivity using temporal correlations in MR images. *Hum Brain Mapp*. 2002; 15(4):247–262. [PubMed: 11835612]
- Happé F, Ehlers S, Fletcher PC, Frith U, Johansson M, Gillberg C, et al. 'Theory of mind' in the brain. Evidence from a PET scan study of Asperger syndrome. *Neuroreport*. 1996; 8:197–201. [PubMed: 9051780]
- Hardan AY, Jou RJ, Keshavan MS, Varma R, Minshew NJ. Increased frontal cortical folding in autism: a preliminary MRI study. *Psychiatry Res*. 2004; 131(3):263–268. [PubMed: 15465295]
- Hazlett HC, Poe M, Gerig G, Smith RG, Provenzale J, Ross A, et al. Magnetic resonance imaging and head circumference study of brain size in autism: birth through age 2 years. *Arch Gen Psychiatry*. 2005; 62(12):1366–1376. [PubMed: 16330725]
- Haznedar MM, Buchsbaum MS, Metzger M, Solimando A, Spiegel-Cohen J, Hollander E. Anterior cingulate gyrus volume and glucose metabolism in autistic disorder. *American Journal of Psychiatry*. 1997; 154:1047–1050. [PubMed: 9247387]
- Head, H. *Aphasia and kindred disorders of speech*. Cambridge: Cambridge University Press; 1926.
- Hendry J, DeVito T, Gelman N, Densmore M, Rajakumar N, Pavlosky W, et al. White matter abnormalities in autism detected through transverse relaxation time imaging. *Neuroimage*. 2006; 29(4):1049–1057. [PubMed: 16214373]
- Herbert MR, Russo JP, Yang S, Roohi J, Blaxill M, Kahler SG, et al. Autism and environmental genomics. *Neurotoxicology*. 2006; 27(5):671–684. [PubMed: 16644012]
- Herbert MR, Ziegler DA, Makris N, Filipek PA, Kemper TL, Normandin JJ, et al. Localization of white matter volume increase in autism and developmental language disorder. *Ann Neurol*. 2004; 55(4):530–540. [PubMed: 15048892]
- Hollander E, Anagnostou E, Chaplin W, Esposito K, Haznedar MM, Licalzi E, et al. Striatal Volume on Magnetic Resonance Imaging and Repetitive Behaviors in Autism. *Biol Psychiatry*. 2005; 58(3):226–232. [PubMed: 15939406]
- Horwitz B. The elusive concept of brain connectivity. *Neuroimage*. 2003; 19(2 Pt 1):466–470. [PubMed: 12814595]
- Horwitz B, Rumsey JM, Grady CL, Rapoport SI. The cerebral metabolic landscape in autism: intercorrelations of regional glucose utilization. *Archives of Neurology*. 1988; 45:749–755. [PubMed: 3260481]
- Hughlings-Jackson J. On affections of speech from disease of the brain. *Brain*. 1878; 1:304–330.
- Hutsler JJ, Love T, Zhang H. Histological and Magnetic Resonance Imaging Assessment of Cortical Layering and Thickness in Autism Spectrum Disorders. *Biol Psychiatry*. 2006
- Hyde, JS.; Biswal, BB. Functionally related correlation in the noise. In: Moonen, CTW.; Bandettini, PA., editors. *Functional MRI*. New York: Springer; 1999. p. 263-275.

- Just MA, Cherkassky VL, Keller TA, Kana RK, Minshew NJ. Functional and Anatomical Cortical Underconnectivity in Autism: Evidence from an fMRI Study of an Executive Function Task and Corpus Callosum Morphometry. *Cereb Cortex*. 2006
- Just MA, Cherkassky VL, Keller TA, Minshew NJ. Cortical activation and synchronization during sentence comprehension in high-functioning autism: evidence of underconnectivity. *Brain*. 2004; 127(Pt 8):1811–1821. [PubMed: 15215213]
- Kana RK, Keller TA, Cherkassky VL, Minshew NJ, Just MA. Sentence comprehension in autism: thinking in pictures with decreased functional connectivity. *Brain*. 2006; 129(Pt 9):2484–2493. [PubMed: 16835247]
- Kandel, ER.; Jessell, TM.; Sanes, JR. Sensory experience and the fine tuning of synaptic connections. In: Kandel, ER.; Schwartz, JH.; Jessell, TM., editors. *Principles of Neural Science*. 4th ed. New York: Elsevier; 2000. p. 1115-1130.
- Keller TA, Kana RK, Just MA. A developmental study of the structural integrity of white matter in autism. *Neuroreport*. 2007; 18(1):23–27. [PubMed: 17259855]
- Koshino H, Carpenter PA, Minshew NJ, Cherkassky VL, Keller TA, Just MA. Functional connectivity in an fMRI working memory task in high-functioning autism. *Neuroimage*. 2005; 24(3):810–821. [PubMed: 15652316]
- Kuhn, T. *The Structure of Scientific Revolutions*. Chicago: University of Chicago Press; 1962.
- Kwon H, Ow AW, Pedatella KE, Lotspeich LJ, Reiss AL. Voxel-based morphometry elucidates structural neuroanatomy of high-functioning autism and Asperger syndrome. *Dev Med Child Neurol*. 2004; 46(11):760–764. [PubMed: 15540637]
- Le Bihan D. Looking into the functional architecture of the brain with diffusion MRI. *Nat Rev Neurosci*. 2003; 4(6):469–480. [PubMed: 12778119]
- Lee L, Friston K, Horwitz B. Large-scale neural models and dynamic causal modelling. *Neuroimage*. 2006; 30(4):1243–1254. [PubMed: 16387513]
- Leopold DA, Murayama Y, Logothetis NK. Very slow activity fluctuations in monkey visual cortex: implications for functional brain imaging. *Cereb Cortex*. 2003; 13(4):422–433. [PubMed: 12631571]
- Levitt JG, O'Neill J, Blanton RE, Smalley S, Fadale D, McCracken JT, et al. Proton magnetic resonance spectroscopic imaging of the brain in childhood autism. *Biol Psychiatry*. 2003; 54(12):1355–1366. [PubMed: 14675799]
- Lichtheim L. On aphasia. *Brain*. 1885; 7:433–484.
- Lidzba K, Staudt M, Wilke M, Krageloh-Mann I. Visuospatial deficits in patients with early left-hemispheric lesions and functional reorganization of language: Consequence of lesion or reorganization? *Neuropsychologia*. 2006; 44(7):1088–1094. [PubMed: 16313931]
- Logothetis NK, Pfeuffer J. On the nature of the BOLD fMRI contrast mechanism. *Magn Reson Imaging*. 2004; 22(10):1517–1531. [PubMed: 15707801]
- Lord, C.; Rutter, M.; DiLavore, P.; Risi, S. *Autism Diagnostic Observation Schedule*. Los Angeles: Western Psychological Services; 2001.
- Lowe MJ, Dzemidzic M, Lurito JT, Mathews VP, Phillips MD. Correlations in low-frequency BOLD fluctuations reflect cortico-cortical connections. *Neuroimage*. 2000; 12(5):582–587. [PubMed: 11034865]
- McAlonan GM, Cheung V, Cheung C, Suckling J, Lam GY, Tai KS, et al. Mapping the brain in autism. A voxel-based MRI study of volumetric differences and intercorrelations in autism. *Brain*. 2005; 128(Pt 2):268–276. [PubMed: 15548557]
- Mizuno A, Villalobos ME, Davies MM, Dahl BC, Müller R-A. Partially enhanced thalamo-cortical functional connectivity in autism. *Brain Research*. 2006; 1104(1):160–174. [PubMed: 16828063]
- Müller R-A. The study of autism as a distributed disorder. *Ment Retard Dev Disabil Res Rev*. 2007; 13:85–95. [PubMed: 17326118]
- Müller, R-A. Functional neuroimaging of developmental disorders: Lessons from autism research. In: Hillary, FD.; DeLuca, J., editors. *Functional Neuroimaging in Clinical Populations*. Guilford: (in press)

- Müller R-A, Kleinhaus N, Kemmotsu N, Pierce K, Courchesne E. Abnormal variability and distribution of functional maps in autism: An fMRI study of visuomotor learning. *Am J Psychiatry*. 2003; 160:1847–1862. [PubMed: 14514501]
- Müller R-A, Pierce K, Ambrose JB, Allen G, Courchesne E. Atypical patterns of cerebral motor activation in autism: a functional magnetic resonance study. *Biological Psychiatry*. 2001; 49:665–676. [PubMed: 11313034]
- Nase G, Singer W, Monyer H, Engel AK. Features of neuronal synchrony in mouse visual cortex. *J Neurophysiol*. 2003; 90(2):1115–1123. [PubMed: 12702711]
- Nelson PG, Kuddo T, Song EY, Dambrosia JM, Kohler S, Satyanarayana G, et al. Selected neurotrophins, neuropeptides, and cytokines: developmental trajectory and concentrations in neonatal blood of children with autism or Down syndrome. *Int J Dev Neurosci*. 2006; 24(1):73–80. [PubMed: 16289943]
- O'Leary DD, Borngasser D. Cortical ventricular zone progenitors and their progeny maintain spatial relationships and radial patterning during preplate development indicating an early protomap. *Cereb Cortex*. 2006; 16 Suppl 1:i46–i56. [PubMed: 16766707]
- O'Leary DD, Nakagawa Y. Patterning centers, regulatory genes and extrinsic mechanisms controlling arealization of the neocortex. *Curr Opin Neurobiol*. 2002; 12(1):14–25. [PubMed: 11861160]
- Otsuka H, Harada M, Mori K, Hisaoka S, Nishitani H. Brain metabolites in the hippocampus-amygdala region and cerebellum in autism: an 1H-MR spectroscopy study. *Neuroradiology*. 1999; 41(7):517–519. [PubMed: 10450847]
- Palmen SJ, van Engeland H, Hof PR, Schmitz C. Neuropathological findings in autism. *Brain*. 2004; 127(Pt 12):2572–2583. [PubMed: 15329353]
- Pezawas L, Meyer-Lindenberg A, Drabant EM, Verchinski BA, Munoz KE, Kolachana BS, et al. 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. *Nat Neurosci*. 2005; 8(6):828–834. [PubMed: 15880108]
- Pickett J, London E. The neuropathology of autism: a review. *J Neuropathol Exp Neurol*. 2005; 64(11):925–935. [PubMed: 16254487]
- Pierce K, Courchesne E. Evidence for a cerebellar role in reduced exploration and stereotyped behavior in autism. *Biological Psychiatry*. 2001; 49:655–664. [PubMed: 11313033]
- Pierce K, Haist F, Sedaghat F, Courchesne E. The brain response to personally familiar faces in autism: findings of fusiform activity and beyond. *Brain*. 2004; 127(Pt 12):2703–2716. [PubMed: 15319275]
- Pierce K, Müller R-A, Ambrose JB, Allen G, Courchesne E. Face processing occurs outside the 'fusiform face area' in autism: evidence from functional MRI. *Brain*. 2001; 124:2059–2073. [PubMed: 11571222]
- Piven J, Bailey J, Ranson BJ, Arndt S. An MRI study of the corpus callosum in autism. *American Journal of Psychiatry*. 1997; 154(8):1051–1055. [PubMed: 9247388]
- Popper, KR. *Conjectures and Refutations: The Growth of Scientific Knowledge*. New York: Routledge & Kegan Paul; 1965.
- Quigley M, Cordes D, Turski P, Moritz C, Haughton V, Seth R, et al. Role of the corpus callosum in functional connectivity. *AJNR Am J Neuroradiol*. 2003; 24(2):208–212. [PubMed: 12591635]
- Rakic P. Specification of cerebral cortical areas. *Science*. 1988; 241(4862):170–176. [PubMed: 3291116]
- Rakic, P.; Ang, ESBC.; Breunig, J. Setting the stage for cognition: Genesis of the primate cerebral cortex. In: Gazzaniga, MS., editor. *The Cognitive Neurosciences*. 3rd ed. Cambridge (Mass.): MIT Press; 2004. p. 33-49.
- Raymond GV, Bauman ML, Kemper TL. Hippocampus in autism: a Golgi analysis. *Acta Neuropathologica*. 1996; 91(1):117–119. [PubMed: 8773156]
- Redcay E, Courchesne E. When is the brain enlarged in autism? A meta-analysis of all brain size reports. *Biol Psychiatry*. 2005; 58(1):1–9. [PubMed: 15935993]
- Rippon G, Brock J, Brown C, Boucher J. Disordered connectivity in the autistic brain: Challenges for the 'new psychophysiology'. *Int J Psychophysiol*. 2006

- Ritvo ER, Freeman BJ, Scheibel AB, Duong T, Robinson H, Guthrie D, et al. Lower Purkinje cell counts in the cerebella of four autistic subjects: initial findings of the UCLA-NSAC autopsy research report. *American Journal of Psychiatry*. 1986; 143:862–866. [PubMed: 3717426]
- Rizzolatti G, Craighero L. The mirror-neuron system. *Annu Rev Neurosci*. 2004; 27:169–192. [PubMed: 15217330]
- Rodier PM. Converging evidence for brain stem injury in autism. *Dev Psychopathol*. 2002; 14(3):537–557. [PubMed: 12349873]
- Rodier PM, Ingram JL, Tisdale B, Nelson S, Romano J. Embryological origin for autism: developmental anomalies of the cranial nerve motor nuclei. *Journal of Comparative Neurology*. 1996; 370:247–261. [PubMed: 8808733]
- Rojas DC, Camou SL, Reite ML, Rogers SJ. Planum temporale volume in children and adolescents with autism. *J Autism Dev Disord*. 2005; 35(4):479–486. [PubMed: 16134033]
- Rubenstein JL, Merzenich MM. Model of autism: increased ratio of excitation/inhibition in key neural systems. *Genes Brain Behav*. 2003; 2(5):255–267. [PubMed: 14606691]
- Ryu YH, Lee JD, Yoon PH, Kim DI, Lee HB, Shin YJ. Perfusion impairments in infantile autism on technetium-99m ethyl cysteinate dimer brain single-photon emission tomography: comparison with findings on magnetic resonance imaging. *European Journal of Nuclear Medicine*. 1999; 26(3):253–259. [PubMed: 10079316]
- Sadato N, Okada T, Honda M, Yonekura Y. Critical period for cross-modal plasticity in blind humans: a functional MRI study. *Neuroimage*. 2002; 16(2):389–400. [PubMed: 12030824]
- Schlaggar B, O'Leary D. Potential of visual cortex to develop an array of functional units unique to somatosensory cortex. *Science*. 1991; 252:1556–1560. [PubMed: 2047863]
- Schmahmann, JD.; Pandya, DN. *Fiber pathways of the brain*. Oxford: Oxford University Press; 2006.
- Schultz RT, Gauthier I, Klin A, Fulbright RK, Anderson AW, Volkmar F, et al. Abnormal ventral temporal cortical activity during face discrimination among individuals with autism and Asperger syndrome [see comments]. *Archives of General Psychiatry*. 2000; 57(4):331–340. [PubMed: 10768694]
- Schumann CM, Amaral DG. Stereological analysis of amygdala neuron number in autism. *J Neurosci*. 2006; 26(29):7674–7679. [PubMed: 16855095]
- Sears LL, Vest C, Mohamed S, Bailey J, Ranson BJ, Piven J. An MRI study of the basal ganglia in autism. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 1999; 23(4):613–624. [PubMed: 10390720]
- Shallice, T. *From Neuropsychology to Mental Structure*. Cambridge: Cambridge UP; 1988.
- Sherman, SM.; Guillery, RW. *Exploring the thalamus*. San Diego: Academic Press; 2001.
- Signoret JL, Castaigne P, Lhermitte F, Abelanet R, Lavorel P. Rediscovery of Leborgne's brain: anatomical description with CT scan. *Brain Lang*. 1984; 22(2):303–319. [PubMed: 6378319]
- Sparks BF, Friedman SD, Shaw DW, Aylward EH, Echelard D, Artru AA, et al. Brain structural abnormalities in young children with autism spectrum disorder. *Neurology*. 2002; 59(2):184–192. [PubMed: 12136055]
- Starkstein SE, Vazquez S, Vrancic D, Nanclares V, Manes F, Piven J, et al. SPECT findings in mentally retarded autistic individuals. *J Neuropsychiatry Clin Neurosci*. 2000; 12(3):370–375. [PubMed: 10956571]
- Sur M, Leamey CA. Development and plasticity of cortical areas and networks. *Nat Rev Neurosci*. 2001; 2(4):251–262. [PubMed: 11283748]
- Sur M, Pallas SL, Roe AW. Cross-modal plasticity in cortical development: differentiation and specification of sensory neocortex. *Trends in Neuroscience*. 1990; 13:227–233.
- Sur M, Schummers J, Dragoi V. Cortical plasticity: time for a change. *Curr Biol*. 2002; 12(5):R168–R170. [PubMed: 11882305]
- Thatcher RW, Walker RA, Giudice S. Human cerebral hemispheres develop at different rates and ages. *Science*. 1987; 236:1110–1113. [PubMed: 3576224]
- Thomas M, Karmiloff-Smith A. Are developmental disorders like cases of adult brain damage? Implications from connectionist modeling. *Behavioral and Brain Sciences*. 2002; 25(6):727–750. [PubMed: 14598624]

- Tsatsanis KD, Rourke BP, Klin A, Volkmar FR, Cicchetti D, Schultz RT. Reduced thalamic volume in high-functioning individuals with autism. *Biol Psychiatry*. 2003; 53(2):121–129. [PubMed: 12547467]
- Turner KC, Frost L, Linsenbardt D, McIlroy JR, Müller R-A. Atypically diffuse functional connectivity between caudate nuclei and cerebral cortex in autism. *Behavioral and Brain Functions*. 2006; 2:34–45. [PubMed: 17042953]
- Uhlhaas PJ, Singer W. Neural synchrony in brain disorders: relevance for cognitive dysfunctions and pathophysiology. *Neuron*. 2006; 52(1):155–168. [PubMed: 17015233]
- Vidal CN, Nicolson R, Devito TJ, Hayashi KM, Geaga JA, Drost DJ, et al. Mapping Corpus Callosum Deficits in Autism: An Index of Aberrant Cortical Connectivity. *Biol Psychiatry*. 2006
- Villalobos ME, Mizuno A, Dahl BC, Kemmotsu N, Müller R-A. Reduced functional connectivity between V1 and inferior frontal cortex associated with visuomotor performance in autism. *Neuroimage*. 2005; 25:916–925. [PubMed: 15808991]
- von Melchner L, Pallas SL, Sur M. Visual behaviour mediated by retinal projections directed to the auditory pathway. *Nature*. 2000; 404(6780):871–876. [PubMed: 10786793]
- Waiter GD, Williams JH, Murray AD, Gilchrist A, Perrett DI, Whiten A. Structural white matter deficits in high-functioning individuals with autistic spectrum disorder: a voxel-based investigation. *Neuroimage*. 2005; 24(2):455–461. [PubMed: 15627587]
- Welchew DE, Ashwin C, Berkouk K, Salvador R, Suckling J, Baron-Cohen S, et al. Functional disconnectivity of the medial temporal lobe in Asperger's syndrome. *Biol Psychiatry*. 2005; 57(9):991–998. [PubMed: 15860339]
- Wernicke, C. *Der aphasische Symptomenkomplex*. repr. 1974 ed.. Berlin: Springer; 1874.
- Williams JH, Whiten A, Suddendorf T, Perrett DI. Imitation, mirror neurons and autism. *Neurosci Biobehav Rev*. 2001; 25(4):287–295. [PubMed: 11445135]
- Wilson TW, Rojas DC, Reite ML, Teale PD, Rogers SJ. Children and Adolescents with Autism Exhibit Reduced MEG Steady-State Gamma Responses. *Biol Psychiatry*. 2006
- Xiong J, Parsons LM, Gao JH, Fox PT. Interregional connectivity to primary motor cortex revealed using MRI resting state images. *Hum Brain Mapp*. 1999; 8(2–3):151–156. [PubMed: 10524607]