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Why the frontal cortex in autism might be talking only to itself: local over-connectivity but long-distance disconnection

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Although it has long been thought that frontal lobe abnormality must play an important part in generating the severe impairment in higher-order social, emotional and cognitive functions in autism, only recently have studies identified developmentally early frontal lobe defects. At the microscopic level, neuroinflammatory reactions involving glial activation, migration defects and excess cerebral neurogenesis and/or defective apoptosis might generate frontal neural pathology early in development. It is hypothesized that these abnormal processes cause malformation and thus malfunction of frontal minicolumn microcircuitry. It is suggested that connectivity within frontal lobe is excessive, disorganized and inadequately selective, whereas connectivity between frontal cortex and other systems is poorly synchronized, weakly responsive and information impoverished. Increased local but reduced long-distance cortical–cortical reciprocal activity and coupling would impair the fundamental frontal function of integrating information from widespread and diverse systems and providing complex context-rich feedback, guidance and control to lower-level systems.

Addresses

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Introduction

Autism is a disorder of brain development, and yet after 60 years of research, remarkably little is known about the underlying developmental neural defects that cause autistic behavior to emerge during the first years of life. Even more startling is that the least is known about the brain region most likely to be centrally involved: frontal cortex.

The hypothesis that frontal lobe abnormality plays a key part in autism has been espoused by researchers during the past quarter century [1,2,3[•]]. This is not surprising

because frontal cortex plays vital roles in higher-order cognitive, language, social and emotion functions [4], each of which is seriously deficient in autism [5]. For example, individuals with autism are typically unable to surmise what another person is thinking [6] or might respond perseveratively once they are taught a particular set of rules [7]. Even within the first years of life, infants with autism show some signs of frontal lobe dysfunction, including abnormalities in social attention and a failure to show the normal trajectory of speech and nonspeech communication development [8–13].

In the past, support for the frontal lobe hypothesis of autism has depended nearly exclusively on inferential behavioral evidence because there has been a near absence of developmental anatomical and microstructural data.

Here, we review the first studies to provide magnetic resonance imaging (MRI) information about early growth abnormalities in frontal lobes in autism [14,15^{••}], and new postmortem data that have provided the first quantitative and regional information about minicolumn maldevelopment in frontal cortex [16–17] and have identified the presence of activated glia and neuroinflammatory response in frontal and cerebellar cortices [18^{••}]. Taken together, these new MRI and postmortem anatomical studies — in conjunction with existent neurofunctional, MRI and postmortem results from older autistic patients — suggest that, just as the autistic child is unable to effectively reciprocally interact with his or her social environment, the frontal cortex in autism is deficient in reciprocally interacting with other cortical regions. Instead, it appears that in early development, frontal cortex in autism might be abnormally over-connected with itself.

Macroscopic evidence of early frontal maldevelopment

Recent studies have discovered that although infants who will eventually develop autism are born with normal to slightly smaller than normal brain sizes, soon thereafter the brain grows at an excessive rate, leaving the autistic toddler with an enlarged brain volume [19,20^{••},21]. Excessive rates of brain growth, however, are not maintained and are followed by slowed or arrested growth ([19], see Courchesne and Pierce [22] for a review). Investigations of which brain regions might be driving the early enlargement of brain volumes have revealed that frontal lobes are the site of the peak of early growth pathology [14,15^{••}]. Frontal lobe gray and white matter

are both disproportionately deviant in size in relation to other cortical areas [14]. Although studies with slightly older children (i.e. older than 7 years) conclude that increases in cerebral white matter volume, particularly frontal cortex, contribute largely to this overall volume increase [23[•]], other studies that include younger subjects find that both gray and white matter are enlarged [14,15^{••}].

Recent structural imaging results on older autistic children are compatible with evidence of pronounced frontal gray and white matter abnormalities in autistic toddlers. With the advent of diffusion tensor imaging (DTI) techniques, white matter fiber tracts can be more thoroughly scrutinized. Fractional anisotropy is a measure in DTI research that reflects the diameter and density of fibers, myelination and macrostructural features such as fiber tract coherence. A recent DTI study reported abnormally reduced fractional anisotropy in white matter adjacent to dorsal and mesial prefrontal cortices in older autistic children [24[•]]. In an effort to further characterize white matter defects in autism, one study subdivided white matter into internal and external compartments and found that it is predominantly the outer radiate portion of white matter, particularly in the frontal lobes, that is disturbed in older autistic children [23[•]]. Furthermore, frontal and temporal sulci are abnormally shifted superiorly and posteriorly in autistic children [25], and frontal cortex has increased gyrification [26].

Whereas several functional imaging studies have shown relatively normal function of primary sensory cortices in autism [27[•],28[•],29], studies rarely report normal functional responding in the frontal lobes. For example, in a sample of autistic patients Pierce *et al.* [27[•]] reported normal functional activity in ventral temporal regions, but not the frontal lobes, in response to personally familiar faces. Abnormalities in frontal responding in autism have also been noted in response to theory of mind [30,31], memory [32,33], attention [34], embedded figures [29] and language tasks [35].

The structural and functional abnormalities that are noted in the frontal lobes in autism probably disturb the efficient interactions of this region with the rest of the brain. In a positron emission tomography (PET) study in 1988, Horwitz *et al.* [36] found reduced correlations among frontal cortex, parietal and other brain regions and concluded that autism involves reduced and impaired functional connectivity between frontal cortex and other lower level brain systems. Since then, there has been disagreement as to whether autism is a disorder of neural underconnectivity [35], overconnectivity [37] or both, in which local connectivity is abnormally increased whereas long-distance connectivity is reduced or abnormally patterned [22,33,38,39].

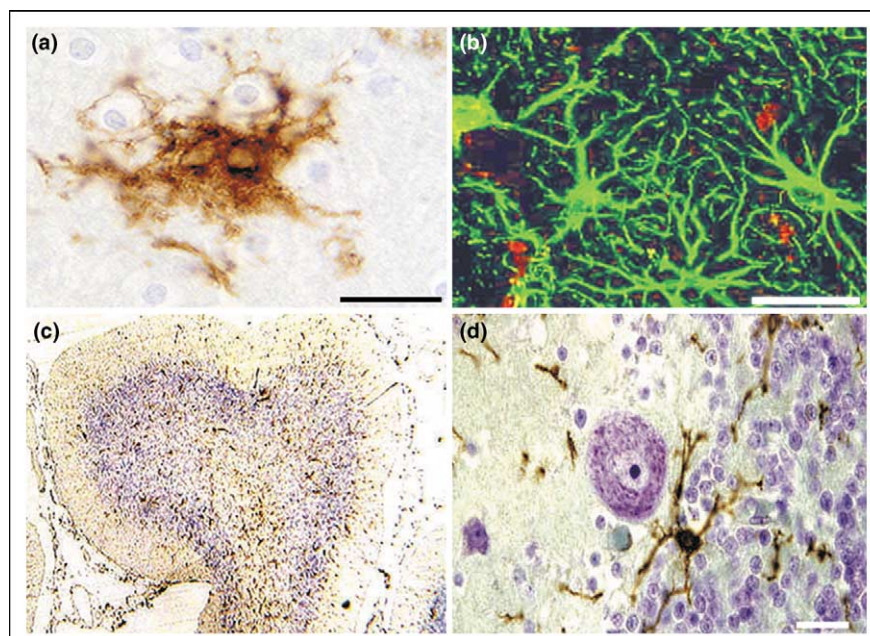
Microscopic evidence of frontal maldevelopment in process

In contrast to the clear new MRI evidence of early frontal growth abnormality and a wealth of behavioral and neurofunctional evidence of frontal dysfunction, there remains a glaring gap in our knowledge of the microstructural defects that disarrange frontal neural circuit development, generate the macroscopic overgrowth of frontal gray and white matter and cause abnormal frontal-mediated behavior. New quantitative microscopic studies, in conjunction with clues from older visual inspection-based reports on the postmortem autistic brain, mark a turning point in our current understanding of the contributions of the early frontal maldevelopment to this disorder.

In arguably the most important postmortem study of autism to date, Vargas *et al.* [18^{••}] reported the first microscopic evidence of maldevelopment in process in the frontal lobe and cerebellum. As illustrated in Figure 1, robust molecular and cellular evidence of an ongoing neuroinflammatory response was found in the gray and white matter of both structures. Specific signs included the presence of activated astroglia with enlarged cell bodies and processes. Microglial activation was pan-laminar in the dorsal and mesial regions of frontal cortex that were studied, and was especially prominent at the junction of cortex and the underlying white matter. In the cerebellum, glial activation was associated with degenerating Purkinje neurons, granule cells and axons, and, in most of the cases examined, there was Purkinje and granule cell loss. Degenerating Purkinje cells were strongly immunoreactive for tumor growth factor- β 1 (TGF- β 1). Prevalent cytokines were macrophage chemoattractant protein (MCP-1) and TGF- β 1 derived from glia. In the same study, cerebrospinal fluid (CSF) taken from living autistic children also showed a marked increase in MCP-1. There was no evidence of an adaptive immune reaction (e.g. T-cell infiltration; deposition of immunoglobulin) in the autistic brains. Findings were present from the youngest age studied, 5 years, to the oldest, 44 years, and present regardless of history of epilepsy, IQ level or history of developmental regression.

The link between abnormal neuroinflammatory response and early brain overgrowth in autism is unknown. Vargas *et al.* [18^{••}] suggest that the presence of activated glia in their child and adult cases could reflect the persistence of a fetal state or process; they also suggest this could be in response to genetic or environmental factors. If fetal glial activation does persist into postnatal life in autism, then perhaps the brain in the autistic infant and toddler is larger than normal because, unlike the normal brain, it continues to have numerous enlarged activated glia because of a genetic-based developmental abnormality. Another possibility is that brain overgrowth in autism is

Figure 1



Glial activation in the frontal cortex (a,b) and cerebellum (c,d) of autistic patients. **(a)** Cluster of activated microglia in frontal cortex visualized with diaminobenzidine tetrahydrochloride chromogen and **(b)** activated astroglia visualized with double immunocytochemical staining for microglia (red) and astroglia (green) using laser confocal imaging. Astroglial reactions were characterized by an increase in the volume of perikarya and glial processes. No glial activations were found in control brain tissues (images not shown). **(c)** Marked activation of microglia was also found in the cerebellum (immunostained with anti-HLA-DR antibody). **(d)** Activated microglia around a Purkinje cell immunostained with HLA-DR. Adapted with permission from Vargas *et al.* [18**]. Reprinted with permission of John Wiley & Sons, Inc.

the result of the response of the brain to environmental factors that trigger a neuroinflammatory reaction; such a reaction would include glial activation and might also include a compensatory production of new neurons and glia [40]. Activation and new production of neurons and glia would abnormally increase brain size. An important question is whether or not the quantitative map of cortical areas with glial activation and neuroinflammation parallels the MRI-based maps of gray and white matter overgrowth and arrest of growth.

A cortical minicolumn is a fundamental unit of cerebral cortical information processing. It is a roughly columnar vertical assembly of pyramidal neurons and interneurons, their interconnections and input and output axons that extends from layer 6 up to the cortical surface [41]. In humans, minicolumns in frontal association cortex are nearly twice the diameter and several times the volume of those in primary sensory cortex, such as primary visual cortex [41]. According to a recent study, by as young as 3 years of age in autism, minicolumns and their surrounding neuropil space are abnormally small throughout frontal but not occipital cortex [17]. This result extends the earlier finding of abnormally narrow minicolumns and surrounding neuropil space in one frontal Brodmann's region (area 9) in older children and adults with autism [16].

Buxhoeveden and colleagues also found that within minicolumns the gray level index was greater than normal, apparently because neurons were too numerous and too small [17]. This excess could reflect defects in the regulation of neurogenesis, delays and defects in apoptosis, perhaps involving glial dysfunction, or a late compensatory phase of neural (and glial) genesis consequent to a late prenatal or early postnatal adverse event. An excess number of cerebral neurons, which means an excess number of axons and collaterals, could be one factor generating early brain overgrowth.

Based on visual inspection, one older study [42] reported the presence of increased neuron density and small neuron size in frontal cingulate cortex in nine out of nine autistic cases. Another postmortem study of 6 autism cases [43] reported that the cortex was abnormally thick in two, lamina were disorganized in two, pyramidal neurons were disoriented in two, and neuron density was increased in three. In an unpublished study, Kennedy and colleagues observed in a 3 year old autistic case, which is also reported in the new minicolumn study mentioned above, a variety of developmental defects in frontal cortex, including clusters of neurons arrested in migration within the cortex, laminar disorganization and disorientation of pyramidal neurons (D. Kennedy, K. Semendeferi, E. Courchesne, pers comm).

It is a realistic possibility that reported glial and neuronal abnormalities in these various studies are connected. Glial cells are involved in apoptosis, neural migration, axon guidance, and minicolumn structural and functional development [44–46]. Disruption of glial development and chronic glial activation during brain development could alter any one or each of these processes, and thereby potentially affect neuron numbers, the regions and lamina that neurons migrate to, axon connectivity patterns, neuronal and synaptic development and functioning, and the organization of cell assemblies within minicolumns. A prenatal or early postnatal disruption of glial and neuron development could have a powerful impact on neuron circuitry within minicolumns, across frontal cortical subregions, and between frontal cortex and other systems, because frontal neural circuitry is quite sparse at birth and takes many years to be fully formed [47–49]. From the neural constructivist perspective [47,48], early neural defects should produce aberrant connectivity and activity, and in turn, such abnormal activity will lead to further abnormal structural development.

What is clear from postmortem evidence is that microcircuitry within minicolumns in autism must be abnormal. Neuroinflammation, migration, neurogenesis and apoptosis abnormalities could each cause a variety of defects including: fractionated and incompletely or aberrantly formed minicolumn vertical circuitry (which could explain why they appear to be too narrow or underdeveloped); an excess of neurons in some layers and a deficit in others within each minicolumn; an excess of neurons in some minicolumns but reduction in others; and, finally, an imbalance between excitation and inhibition (as hypothesized by Rubenstein and Merzenich [50^{*}]) within and between minicolumns.

These defects in turn might alter local as well as long-distance frontal cortical connectivity and functional differentiation. Reduced inhibitory control over excitatory activity [50^{*}] within and between minicolumns could undermine the development of functionally discrete minicolumns — that is, minicolumn functional boundaries could become blurred and responding could be abnormally under-selective. It would also tend to enable local excitation to last too long and spread too far across local patches of cortex. Such unmodulated firing of cells and minicolumns across local and short-distance patches of cortex would tend to favor retaining an abnormal number and pattern of local and short-distance connections. Conversely, it would tend to reduce the temporal and spatial resolution of processing of input from distant sources, and it would reduce the degree of synchrony of bursts of firing between clusters of minicolumns in two or more distant regions such as frontal and parietal. Long-distance cortical–cortical coupling, which is dependent on precisely timed reciprocal oscillatory signaling, would be impaired and connectivity lost. Thus, during the first

years of development, activity-dependent processes would tend to produce an increased number of abnormal local and short-distance connections but a reduced number of long-distance frontal–posterior and posterior–frontal connections.

Developmentally early defects in minicolumn microcircuitry in frontal cortex could explain why higher order frontal processes fail to appear in autistic toddlers, why frontal control and guidance over lower-level systems fails to develop adequately, why frontal cortex does not get activated normally, and why frontal activity is not correlated with activity in other cortical and subcortical systems.

Conclusions

For more than two decades it has been clear that frontal lobe abnormality must be an important factor underlying core features of autism, including severe impairment in higher order social and emotional processing and communication, cognitive functions, orienting to and exploring the social and non-social world, and speech. Neuroimaging studies of older children and adults with autism have demonstrated reduced or deviant frontal cortical neural activity. Since first discovered and interpreted by Horwitz *et al.* [36], it has also been clear that frontal cortical activity is not correlated with activity in parietal and other cortical subcortical systems, and that this failure indicates impaired frontal connections with and control over lower-level systems. Shrouded in mystery, however, has been the early developmental origin of frontal functional impairment.

For the first time, studies reveal early developmental abnormalities at both the macroscopic and the microscopic levels in the first years of life, and the frontal lobes are the peak cerebral sites of pathology. At the microscopic level, frontal neural pathology involves neuroinflammation, migration defects, and excess cerebral neurogenesis and/or defective apoptosis. It is hypothesized that these abnormal processes cause malformation and, therefore, malfunction of frontal minicolumn microcircuitry. It is suggested that this results in abnormally patterned and increased local and short-distance frontal cortical connectivity, but reduced long-distance reciprocal connectivity between frontal cortex and other brain regions. Reduced long-distance cortical–cortical reciprocal activity and coupling would impair the fundamental frontal function of integrating information from widespread and diverse systems (emotional, language, sensory, autonomic, etc) and provide complex context-rich feedback, guidance and control to lower-level systems. Overall, aberrantly heightened local frontal excitability in conjunction with impaired long-distance frontal cortical coupling with distant systems would explain why frontal activity is poorly selective, often does not show differentiation between task conditions and is commonly

reported to be poorly correlated with posterior cortical activity.

We speculate that from the first years of life frontal cortex — metaphorically speaking — talks with itself but fails to hear and respond to other brain systems. Connectivity within the frontal lobe is excessive, disorganized, hyperactive and poorly selective. That is, within the frontal lobe, connectivity is excessive but disorganized and poorly selective. Conversely, between frontal cortex and other systems, connectivity is reduced, unsynchronized, weakly responsive and information impoverished. The toddler with autism struggles to make sense of a complex social and non-social world with powerful lower-level processing potential but with a frontal cortex that is functionally disorganized, noisy, and effectively ‘disconnected’. The original causes that trigger a cascade of maldevelopment leading to this neurofunctional impasse remain to be determined, but a major clue might be the recent identification of an ongoing neuroinflammatory response with glial activation [18**].

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Damasio AR, Maurer RG: **A neurological model for childhood autism.** *Arch Neurol* 1978, **35**:777-786.
2. Ozonoff S: **Executive functions in autism.** In *Learning and Cognition in Autism. Current Issues in Autism.* Edited by Schopler E, Mesibov GB. Plenum Press; 1995:199-219.
3. Mundy P: **Annotation: the neural basis of social impairments in autism: the role of the dorsal medial-frontal cortex and anterior cingulate system.** *J Child Psychol Psychiatry* 2003, **44**:793-809.
- The author provides a thorough review of the dorsal medial frontal cortex and anterior cingulate cortex and their role in the pathology of autism.
4. Stuss D, Knight R: *Principles of Frontal Lobe Function.* Oxford University Press; 2002.
5. Kanner L: **Autistic disturbances of affective contact.** *Nervous Child* 1943, **2**:217-250.
6. Baron-Cohen S: **The development of a theory of mind in autism: deviance and delay?** *Psychiatr Clin North Am* 1991, **14**:33-51.
7. Ozonoff S, Pennington BF, Rogers SJ: **Executive function deficits in high-functioning autistic individuals: relationship to theory of mind.** *J Child Psychol Psychiatry* 1991, **32**:1081-1105.
8. Rogers SJ, Di Lalla D: **Age of symptom onset in young children with pervasive developmental disorders.** *J Am Acad Child Adolesc Psychiatry* 1990, **29**:863-872.
9. Baron-Cohen S, Allen J, Gillberg C: **Can autism be detected at 18 months? The needle, the haystack, and the CHAT.** *Br J Psychiatry* 1992, **161**:839-843.
10. Dawson G, Osterling J, Meltzoff AN, Kuhl P: **Case study of the development of an infant with autism from birth to two years of age.** *J Appl Dev Psychol* 2000, **21**:299-313.
11. Lord C, Risi S: **Diagnosis of autism spectrum disorders in young children.** In *Autism Spectrum Disorders: A Transactional Developmental Perspective.* Edited by Wetherby A, Prizant B, Paul H. Brookes Publishing Co; 2000:167-190.
12. Maestro S, Muratori F, Cavallaro MC, Pei F, Stern D, Golse B, Palacio-Espasa F: **Attentional skills during the first 6 months of age in autism spectrum disorder.** *J Am Acad Child Adolesc Psychiatry* 2002, **41**:1239-1245.
13. Wetherby AM, Woods J, Allen L, Cleary J, Dickinson H: **Early indicators of autism spectrum disorders in the second year of life.** *J Autism Dev Disord* 2004, **34**:473-493.
14. Carper RA, Moses P, Tigue ZD, Courchesne E: **Cerebral lobes in autism: early hyperplasia and abnormal age effects.** *Neuroimage* 2002, **16**:1038-1051.
15. Carper R, Courchesne E: **Localized enlargement of the frontal lobe in autism.** *Biol Psychiatry* 2005, **57**:126-133.
- This study demonstrated that in autism, overgrowth within the frontal lobes is localized to dorsal and mesial regions by early childhood. In autism, this early regionally localized frontal overgrowth is followed by abnormally slow frontal growth, whereas in normal children, frontal growth continues at a robust pace throughout childhood (autism versus normal: 10% versus 48% increase in frontal volumes between 2 and 9 years of age). Combined with past data, the authors conclude that early overgrowth might be more marked in later developing association cortices than in early developing lower-level systems.
16. Casanova MF, Buxhoeveden DP, Switala AE, Roy E: **Minicolumnar pathology in autism.** *Neurology* 2002, **58**:428-432.
17. Buxhoeveden D, Semendeferi K, Schenker N, Courchesne E: **Decreased cell column spacing in autism [abstract].** *Soc Neurosci* 2004:582.6.
18. Vargas DL, Nascimbene C, Krishnan C, Zimmerman AW, Pardo CA: **Neuroglial activation and neuroinflammation in the brain of patients with autism.** *Ann Neurol* 2005, **57**:67-81.
- The authors documented the first direct evidence of immune-mediated mechanisms in the neuropathology of autism. Autopsy tissue from 11 autistic patients was used for immunocytochemistry studies. Results showed active neuroinflammatory processes in frontal cortex, underlying white matter and cerebellum as noted by glial activation patterns. Future therapies for autism might thus involve modifying neuroglia responses in the brain.
19. Courchesne E, Karns C, Davis HR, Ziccardi R, Carper R, Tigue Z, Pierce K, Moses P, Chisum HJ, Lord C *et al.*: **Unusual brain growth patterns in early life in patients with autistic disorder: an MRI study.** *Neurology* 2001, **57**:245-254.
20. Courchesne E, Carper R, Akshoomoff N: **Evidence of brain overgrowth in the first year of life in autism.** *JAMA* 2003, **290**:337-344.
- This study provided clear evidence that brain growth dysregulation begins shortly after birth in infants who will eventually develop autism. In this study, head circumference (HC) was slightly smaller at birth in autistic infants, but by 6–14 months of age increased to the 84th percentile or greater. This study highlights the potential of using changes in HC as a neurobiological early warning sign of autism. The authors suggest a strong need for further study on the causes of abnormal brain growth in autism.
21. Sparks BF, Friedman SD, Shaw DW, Aylward E, Echelard D, Artru AA, Maravilla KR, Giedd JN, Munson J, Dawson G *et al.*: **Brain structural abnormalities in young children with autism spectrum disorder.** *Neurology* 2002, **59**:184-192.
22. Courchesne E, Pierce K: **Early brain overgrowth in autism: a potential signal of disrupted development of frontal pyramidal neurons and cortical connectivity.** *Int J Dev Neurosci* in press.
23. Herbert MR, Ziegler DA, Makris N, Filipek PA, Kemper TL, Normandin JJ, Sanders HA, Kennedy DN, Caviness VS Jr: **Localization of white matter volume increase in autism and developmental language disorder.** *Ann Neurol* 2004, **55**:530-540.
- This study further characterizes white matter defects in autism by showing that only the later myelinating outer white matter (called ‘radiate’ white

matter) compartments are enlarged, with deviations from normal being greatest in frontal lobes. Radiate white matter myelinates later than deep white matter and is thus consistent with reports of postnatal brain overgrowth in autism. The authors also found a similar pattern of white matter abnormality in developmental language disorder subjects and argue that the underlying pathophysiology might be similar for the two disorders.

24. 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**:323-326.
Using DTI, the authors found abnormalities in white matter underlying frontal cortices involved in social functioning.
25. Levitt JG, Blanton RE, Smalley S, Thompson PM, Guthrie D, McCracken JT, Sadoun T, Heinichen L, Toga AW: **Cortical sulcal malp in autism.** *Cereb Cortex* 2003, **13**:728-735.
26. Hardan AY, Jou RJ, Keshavan MS, Varma R, Minshew NJ: **Increased frontal cortical folding in autism: a preliminary MRI study.** *Psychiatry Res* 2004, **131**:263-268.
27. 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**:2703-2716.
This fMRI study highlights the frontal lobes as a major site of abnormal neurofunctional responding. Although the majority of primary sensory cortices (e.g. visual cortex) showed normal functional responding to faces, there was a notable omission in the medial frontal cortex in the autism group. Furthermore, this study disputes the long held notion that the 'fusiform face area' is deficient in autism and proposes that defects in face processing are the result of influences from abnormalities in other systems, such as attention.
28. Hadjikhani N, Chabris C, Joseph R, Clark J, McGrath L, Aharon I, Feczko E, Tager-Flusberg H, Harris G: **Early visual cortex organization in autism: an fMRI study.** *Neuroreport* 2004, **15**:267-270.
This functional imaging study provides support for the idea that the neural structures involved in basic visual processing are intact in autism. The authors speculate that abnormalities in visual processing must therefore emerge from defects in top down processing.
29. Ring HA, Baron-Cohen S, Wheelwright S, Williams SC, Brammer M, Andrew C, Bullmore ET: **Cerebral correlates of preserved cognitive skills in autism: a functional MRI study of embedded figures task performance.** *Brain* 1999, **122**:1305-1315.
30. 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**:1839-1849.
31. Happé F, Ehlers S, Fletcher PC, Frith U, Johansson M, Gillberg C, Dolan RJ, Frackowiak RSJ, Frith CD: **'Theory of mind' in the brain. Evidence from a PET scan study of Asperger syndrome.** *Neuroreport* 1996, **8**:197-201.
32. Luna B, Minshew NJ, Garver KE, Lazar NA, Thulborn KR, Eddy WF, Sweeney JA: **Neocortical system abnormalities in autism: an fMRI study of spatial working memory.** *Neurology* 2002, **59**:834-840.
33. 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**:810-821.
34. Belmonte MK, Yurgelun-Todd DA: **Functional anatomy of impaired selective attention and compensatory processing in autism.** *Brain Res Cogn Brain Res* 2003, **17**:651-664.
35. 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**:1811-1821.
36. Horwitz B, Rumsey JM, Grady CL, Rapoport SI: **The cerebral metabolic landscape in autism. Intercorrelations of regional glucose utilization.** *Arch Neurol* 1988, **45**:749-755.
37. Casanova MF: **White matter volume increase and minicolumns in autism.** *Ann Neurol* 2004, **56**:453,454.
38. Belmonte M, Cook JEH, Anderson G, Rubenstein J, Greenough W, Beckel-Mitchener A, Courchesne E, Boulanger L, Powell S, Levitt P *et al.*: **Autism as a disorder of neural information processing: directions for research and targets for therapy.** *Molecular Psychiatry* 2004, **9**:646-663.
39. Courchesne E: **Brain development in autism: early overgrowth followed by premature arrest of growth.** *Ment Retard Dev Disabil Res Rev* 2004, **10**:106-111.
40. Vaccarino FM, Ment LR: **Injury and repair in developing brain.** *Arch Dis Child Fetal Neonatal Ed* 2004, **89**:F190-F192.
41. Buxhoeveden DP, Casanova MF: **The minicolumn hypothesis in neuroscience.** *Brain* 2002, **125**:935-951.
42. Kemper T, Bauman M: **Neuropathology of infantile autism.** *J Neuropathol Exp Neurol* 1998, **57**:645-652.
43. Bailey A, Luthert P, Dean A, Harding B, Janota I, Montgomery M, Rutter M, Lantos P: **A clinicopathological study of autism.** *Brain* 1998, **121**:889-905.
44. Fields RD, Stevens-Graham B: **New insights into neuron-glia communication.** *Science* 2002, **298**:556-562.
45. Nedergaard M, Ransom B, Goldman SA: **New roles for astrocytes: redefining the functional architecture of the brain.** *Trends Neurosci* 2003, **26**:523-530.
46. Colombo J, Reisin H: **Interlaminar astroglia of the cerebral cortex: a marker of the primate brain.** *Brain Res* 2004, **1006**:126-131.
47. Quartz SR, Sejnowski TJ: **The neural basis of cognitive development: a constructivist manifesto.** *Behav Brain Sci* 1997, **20**:537-556. discussion 556-596.
48. Quartz SR: **The constructivist brain.** *Trends Cogn Sci* 1999, **3**:48-57.
49. Huttenlocher P: *Neural Plasticity: The Effects of Environment on the Development of Cerebral Cortex.* Harvard University Press; 2002.
50. Rubenstein JL, Merzenich MM: **Model of autism: increased ratio of excitation/inhibition in key neural systems.** *Genes Brain Behav* 2003, **2**:255-267.
The authors describe a model of autism that postulates that some forms of the disorder result from an increased ratio of excitation-inhibition in key neural systems regulating sensory, memory, social and emotional functions.