Neuroimaging in Autism Spectrum Disorder

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Abstract

Modern neuroimaging techniques have provided researchers with invaluable tools to explore anatomical and functional brain abnormalities in individuals with autism spectrum disorder (ASD). Converging evidence from structural MRI studies demonstrates differences in post-natal brain maturation in individuals with ASD compared to healthy controls, with early brain overgrowth followed by a subsequent plateauing of growth through adolescence and specific regional brain volume reductions in adulthood. These brain volume reductions occur in regions (e.g. amygdala, cerebellum, corpus callosum) which have been linked repeatedly to the clinical phenotype. Functional MRI, MRI spectroscopy and diffusion tensor imaging studies have further clarified the neurobiology of ASD, with increasing evidence demonstrating brain dysconnectivity and white matter abnormalities. Future longitudinal neuroimaging studies using a variety of neuroimaging techniques aligned to clinical and behavioural data should further clarify the neurobiology of ASD.

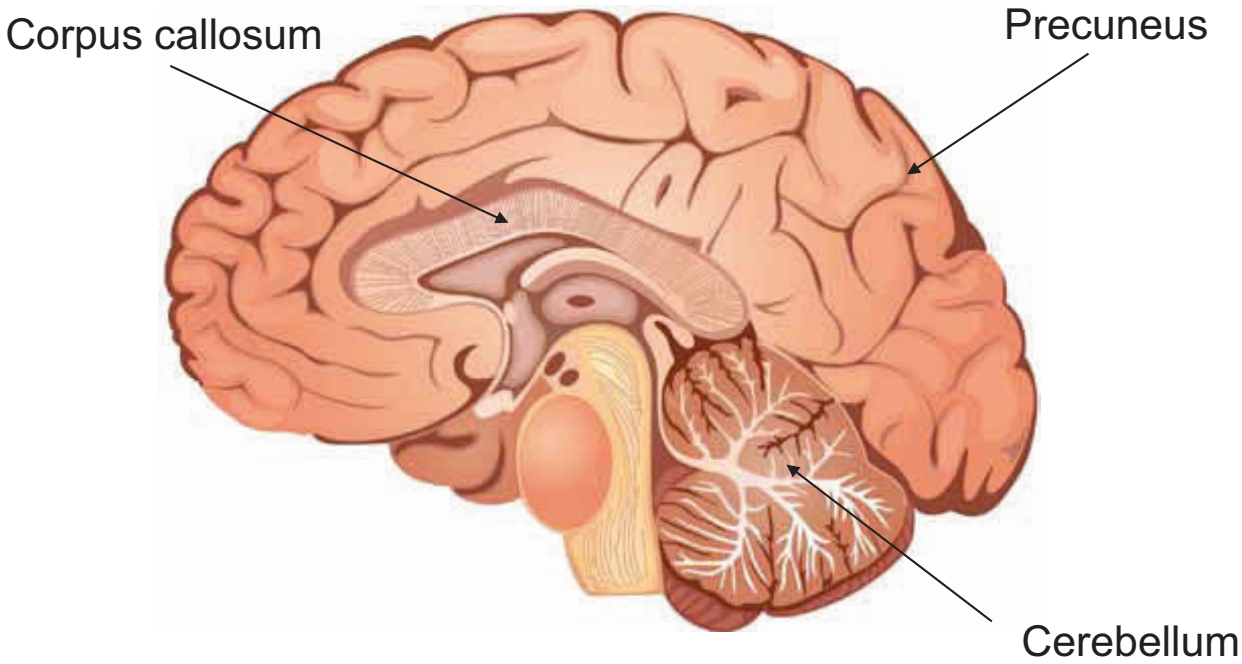
Introduction

Neuroimaging methods have made a valuable contribution to increasing our understanding of the biological basis of autism spectrum disorder (ASD) (1). In this paper, we principally detail structural MRI (sMRI) brain findings in ASD and give a possible clinical rationale for these findings. We also discuss, in brief, some findings relating to magnetic resonance spectroscopy (MRS) and functional MRI (fMRI).

Structural MRI (sMRI) Research Findings

sMRI studies have consistently demonstrated a global increase in brain volume in young children (2-4). However, results from adolescents and adults have been more inconsistent and generally demonstrate no difference in global brain volume between individuals with ASD and healthy controls (5-7). This early brain overgrowth has, in particular, been linked to an increase in white matter in frontal brain regions (8,9) and in the amygdala (10). In adulthood, an increasing body of evidence from both region of interest (ROI) and voxel-based morphometry (VBM) studies, has demonstrated regional brain volume reductions, predominantly in the amygdala-hippocampal complex (11,12), precuneus (12), cerebellum (6,13-15) and corpus callosum (CC) (16), although many other brain regions have also been implicated (Figure 1). In addition, sMRI studies have demonstrated age-related cortical thinning and reduced cortical gyrification, with the parietal lobe, including the precuneus, especially implicated (17-20).

Figure 1. Structural MRI findings in Autism Spectrum Diorders



Interpretation of structural findings

Global Brain Volume

sMRI evidence in ASD indicates that early brain overgrowth is followed by a subsequent plateauing or decline in brain size by early childhood, with ongoing reduction in brain volume from adolescence to late middle age. Evidence demonstrating increased peripheral cerebrospinal fluid (CSF) volume but not increased lateral ventricular volume in adulthood (7) (i.e. potential loss of cortical tissue), and reduced cortical thickness further indicates an abnormal developmental trajectory in individuals with ASD compared to healthy controls. Possible explanations for such an abnormal developmental trajectory include differences in neurotrophin levels, including brain-derived neurotrophic factor (BDNF) and neurotrophin-4 (NT-4), in ASD individuals compared to controls, particularly as higher plasma concentrations have been detected in newborns with ASD (21) and as these neurotrophins can decrease Purkinje cell survival (in the cerebellum) by excitotoxic methods (22). It is not known exactly when this abnormal developmental trajectory commences, with only one study to date examining pre-natal brain size in individuals with ASD, demonstrating no difference compared to healthy controls (23).

Cerebellum

The cerebellum is now known to be important for higher-order functioning, including attention (24), social interaction (25) and executive functioning (26), all areas of relative impairment in individuals with ASD; consequently reductions in cerebellar volume in individuals with ASD may explain these findings. Furthermore, previously normally functioning individuals with acquired cerebellar lesions have displayed social and communicative deficits (27,28) similar to those observed in ASD, and fMRI studies in ASD individuals have demonstrated differences in cerebellar activation compared with controls during motor (29) and social tasks (30).

Limbic System, including the Amygdala

The amygdala and its adjacent brain structures, principally the hippocampus, are components of the limbic system and play a crucial role in mediating social behaviours, including the processing of facial expressions (30), assigning significance to environmental stimuli (31), memory and stress regulation (32), with these structures having a close reciprocal relationship during memory and social tasks (33). Impairments in these social cognition skills are particularly evident in individuals with ASD and may consequently explain the structural brain differences noted. Further evidence implicating the limbic

system in ASD is evident from volume reductions of the fusiform "face area", a region particularly important for processing facial emotions (13).

Precuneus

The precuneus is implicated in social cognition, including self-awareness and empathy (34), processing visuo-spatial imagery and episodic memory, all difficulties evident in individuals with ASD (35, 36).

Corpus Callosum (CC)

The CC is the largest commissural white matter tract in the brain. It is involved in motor and sensory integration in addition to multiple higher-order cognitive functions, including abstract reasoning, planning, attention, language comprehension and social cognition (37), all of which have been demonstrated to be impaired in individuals with ASD. Furthermore, reduced volume of the CC in ASD has been found to correlate with core ASD features, including social deficits, repetitive behaviours and sensory abnormalities (16), as well as executive dysfunction and impairments in complex motor skills (38).

Comparing Autism and Asperger Syndrome

Some ROI and VBM studies (7,12) have demonstrated no differences in regional brain volumes between individuals with autism and Asperger syndrome. However, evidence of variation within the ASD clinical phenotype has also been noted, including increased grey matter in the superior temporal gyrus and inferior parietal lobe in individuals with autism compared to those with Asperger Syndrome (13). These regional brain differences correspond with the main differentiating clinical diagnostic feature, namely developmental language abnormalities.

Gender

The prevalence of ASD is approximately 3 times higher in males compared to females (39), and consequently most neuroimaging studies have been conducted in male-only (or predominantly male) samples, with structural brain anatomy among females with ASD consequently under-investigated. This is despite growing evidence for differences in the clinical phenotype between genders, including a greater ability for females to camouflage their social difficulties (40). Some sMRI studies have, however, investigated females with ASD (41,42) and demonstrated neuroanatomical differences in females with ASD (e.g. limbic system) compared to healthy control females, consistent with those detected in males with ASD. Widespread differences in white matter between genders has been noted in ASD (41), with an increase in cerebellar white matter volume compared to healthy controls noted in females (42), a finding not ascertained in recent research in adult males with ASD. These differences are difficult to interpret but may suggest some variation in brain anatomy related to a variation in the clinical phenotype in females compared to males.

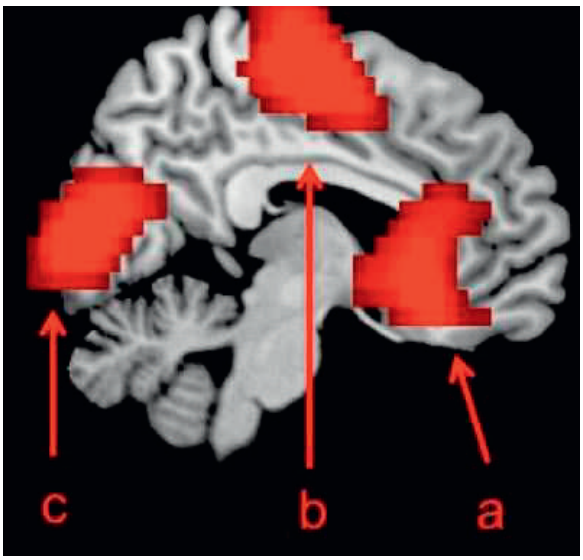
Functional Magnetic Resonance Imaging (fMRI)

fMRI studies have contributed significantly to our understanding of ASD pathology, with numerous fMRI studies examining aspects of social cognition (e.g. theory of mind, face processing), executive function and language demonstrating altered brain activity compared to healthy controls (43-45). fMRI studies have demonstrated impairments in brain networks and decreased functional cortical connectivity between regions of interest (46), with "long-distance" brain disconnectivity in ASD demonstrated by numerous studies investigating a variety of tasks related to core symptoms of ASD, including language (47), social cognition (48) and executive function (49).

In support of sMRI research in ASD, facial emotion processing studies have consistently demonstrated differences in the limbic and "face processing" regions including hypoactivation of the fusiform gyrus and amygdala during facial emotion processing tasks (50,51). However, more recently, a double-blind placebo-controlled crossover trial of acute tryptophan depletion (to reduce serotonin levels) measured brain activity using fMRI in response to a facial emotion processing task and demonstrated

significant differences in the modulation of the processing of facial expressions of emotions across the "social brain network", potentially suggesting that serotonin dysfunction in ASD may be related to this altered brain activity (52).

Figure 2. fMRI and processing of emotional disgust in individuals with ASD compared to controls

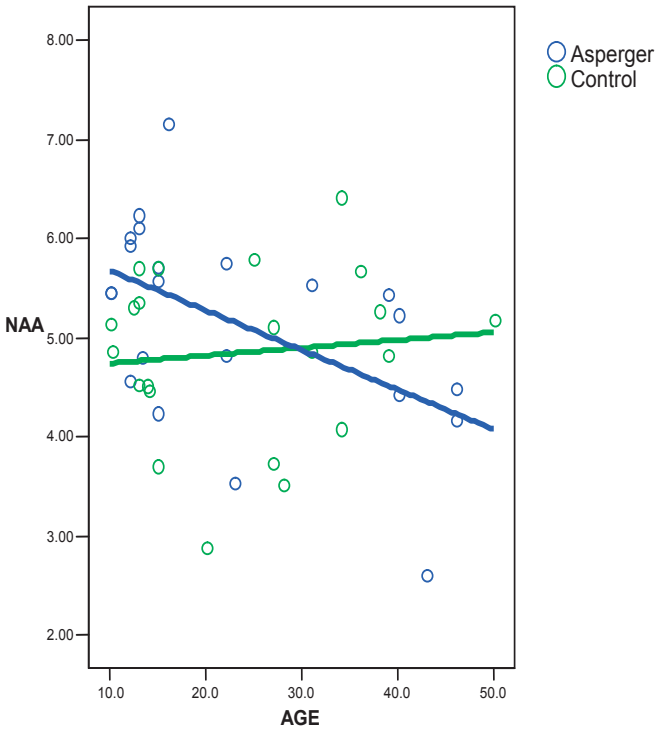


Saggital view of the brain.
Serotonin reduction (using acute tryptophan depletion) was associated with altered levels of activity in the medial frontal gyrus (A and B) and occipital lobe when processing emotion of disgust - brain regions associated with the social brain network.
Adapted from Daly et al., 2012 (56)

Diffusion Tensor Imaging (DTI)
Diffusion Tensor Imaging (DTI) evaluates the structural integrity of specific white matter tracts of interest, by measuring diffusion of water molecules along the axons. A number of studies have demonstrated atypical structural connectivity in individuals with ASD (53). Most commonly, DTI studies have reported widespread increases in mean diffusivity (MD) across the brain (54-56) reflecting poorly-organised white matter. Similarly, decreases in fractional anisotropy (FA), reflecting decreased organisation and coherence in white matter tracts, has been noted in multiple brain regions in both children and adults with ASD (57,58), although increased FA has also been identified in younger children (59) and adolescents (60) with ASD. These findings suggest widespread abnormalities of white matter tracts, with some suggestion of abnormal myelin integrity due to findings of radial diffusivity abnormalities (53).

Magnetic Resonance Spectroscopy (MRS)
Magnetic Resonance Spectroscopy (MRS) has been utilised to examine brain metabolism and neuronal integrity through quantification of a variety of brain metabolites including N-acetyl aspartate (NAA), creatinine, choline and glutamate (or glutamate + glutamine + GABA (Glx)) in brain structures previously implicated in ASD, such as the amygdala-hippocampal complex. Age-related reductions in NAA, a putative marker for neuronal density and/or integrity (61) have been demonstrated in individuals with ASD compared to controls, possibly suggesting differential changes over time in neuronal density and mitochondrial metabolism (Figure 3). Furthermore, decreases in NAA have been linked to social deficits (62), which are core deficits in individuals with ASD. In addition, a recent study has detected reduced glutamate/glutamine (Glu/Gln) and inositol concentrations, both markers of excitatory neurotransmitter regulatory activity in the brain, in the right anterior cingulate cortex and decreased concentration of inositol in the left temporo-parietal junction (63).

Figure 3. Relationship between NAA and Age in people with Asperger syndrome and Controls



(z = 2.101, p = 0.009).
An age-related reduction in NAA in individuals with Asperger Syndrome compared to controls in the amygdala-hippocampal complex is presented above suggesting possible differential changes over time in neuronal density and mitochondrial metabolism.
Adapted from O'Brien et al., 2010 (61)

Conclusion

Modern neuroimaging techniques have substantially expanded our knowledge with respect to the neurobiology of ASD, with evidence of widespread structural and functional brain abnormalities. Future longitudinal neuroimaging studies using a variety of neuroimaging techniques aligned to clinical and behavioural data should further clarify the neurobiology of ASD.

GP Comment.

What have I learned from this paper?

1. Whilst GPs would not be able to arrange these types of neuroimaging in Primary Care, this interesting research clearly shows that autism is a neurobiological disorder and not, as was previously thought, the result of poor parenting.

2. In ASD, differences in brain volume and growth at different ages are noteworthy as are abnormalities in certain brain networks and connectivity. Overall, both structural and functional imaging seem to point to impairments in areas of the brain that are important in social behaviour and understanding. This may help explain some of the issues that GPs may encounter with these individuals.

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References

1. Ecker C, Murphy D. Neuroimaging in autism – from basic science to transitional research. Nat Rev Neuro 2014; 10: 82-91.
2. Courchesne E, Carper R, Akshoomoff N. Evidence of brain overgrowth in the first year of life in autism. JAMA 2003; 290: 337–344.
3. 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: 1366–1376.
4. Carper RA, Moses P, Tigue ZD, Courchesne E. Cerebral lobes in autism: early hyperplasia and abnormal age effects. Neuroimage 2002; 4: 1038-1051.
5. Ecker C, Suckling J, Deoni SC, Lombardo MV, Bullmore ET, Baron- Cohen S, et al. Brain anatomy and its relationship to behavior in adults with autism spectrum disorder: a multicenter magnetic resonance imaging study. Arch Gen Psychiatry 2012; 69:195-209.
6. McAlonan GM, Cheung C, Cheung V, Wong N, Suckling J, Chua SE. Differential effects on white-matter systems in high-functioning autism and Asperger's syndrome. Psychol Med 2009; 39: 1885-1893.
7. Hallahan B, Daly EM, McAlonan G, Loth E, Toal F, O'Brien F, et al. Brian morphometry volume in autistic spectrum disorder: a magnetic resonance imaging study of adults. Psychol Med 2008; 39: 337-346.
8. Courchesne E, Campbell K, Solso S. Brain growth across the lifespan in autism: Age-specific changes in anatomical pathology. Brian Research 2011; 1380:138-145.
9. Herbert MR, Ziegler DA, Deutsch CK, O'Brien LM, Lange N, Bakardjiev A, et al. Dissociations of cerebral cortex, subcortical and cerebral white matter volumes in autistic boys. Brain 2003; 126:1182-192.
10. Amaral DG, Schumann CM, Nordahl CW. Neuroanatomy of autism. Trends Neurosci 2008; 31:137-145.
11. Aylward EH, Minshew NJ, Goldstein G et al. MRI volumes of amygdala and hippocampus in non-mentally retarded autistic adolescents and adults. Neurology 1999; 53: 2145-2150.
12. Via E, Radua J, Cardoner N, Happe F, Mataix-Cols D. Meta-analysis of gray matter abnormalities in Autism Spectrum Disorder. Arch Gen Psychiatry 2011; 68: 409-418.
13. Toal, F, Daly EM, Page L, Deeley Q, Hallahan B, Bloemen O, et al. Clinical and anatomical heterogeneity in autistic spectrum disorder: a structural MRI study. Psychol Med 2010; 40: 1171-1181.
14. McAlonan GM, Cheung V, Cheung C, Suckling J, Lam GY, Tai KS, et al. Mapping the brain in autism. A voxel-based morphometry study of volumetric differences and intercorrelations in autism. Brain 2005; 128: 268-276.
15. Stanfield AC, McIntosh AM, Spencer MD, Philip R, Gaur S, Lawrie SM. Towards a neuroanatomy of autism: a systematic review and meta-analysis of structural magnetic resonance imaging studies. Eur Psychiatry 2008; 23: 289-299.
16. Frazier TW, Hardan AY. A meta-analysis of the corpus callosum in autism. Biol Psychiatry 2009; 66: 935-941.
17. Wallace GL, Dankner N, Kenworthy L, Giedd JN, Martin A. Age-related temporal and parietal cortical thinning in autism spectrum disorders. Brain 2010; 133: 3745–3754.
18. Wallace GL, Robustelli B, Danker N, Kenworthy L, Gledd JN, Martin A. Increased gyrification, but comparable surface area in adolescents with autism spectrum disorders. Brain 2013; 136: 1956-1967.
19. Ecker C, Ginest C, Feng Y, Johnston P, Lombardo MV, Lai MC, et al. Brain surface anatomy in adults with autism: the relationship between surface area, cortical thickness, and autistic symptoms. JAMA Psychiatry 2013; 70: 59-70.
20. Kates WR, Ikuta I, Burnette CP. Gyrification patterns in monozygotic twin pairs varying in discordance for autism. Autism Res 2009; 2: 267-278.
21. Nelson KB, Grether JK, Croen LA, Dambrosia JM Dickens BF, Jelliffe LL, et al. Neuropeptides and neurotrophins in neonatal blood of children with autism or mental retardation. Annals Neurol 2001; 49: 597-606.
22. Morrison ME, Massone CA. Granule neuron regulation of Purkinje cell development: striking a

balance between neurotrophin and glutamate signaling. J Neurosci 1998; 18: 3563-3573.
23. Hobbs K, Kennedy A, Dubray M, et al. A retrospective fetal ultrasound study of brain size in autism Biol Psychiatry 2007; 62: 1048-1055.
24. Allen G, Buxton R Wong EC, Courchesne E. Attentional activation of the cerebellum independent of motor involvement, Science 1997;275: 1940-1943.
25. Townsend J, Courchesne E, Covington J, Westerfield M, Harris NS, Lyden P, et al. Spatial attention deficits in patients with acquired or developmental cerebellar abnormality. J Neurosci 1999; 19: 5632-5643.
26. Ronning C, Sundet K, Due-Tonnessen B, Lundar T, Helseth E. Persistent cognitive dysfunction secondary to cerebellar injury in patients treated for posterior fossa tumours in childhood. Pediatr Neurosurg 2005; 41: 15-21.
27. Schmahann JD, Sherman JC. The cerebellar cognitive affective syndrome. Brain 1998; 121: 561-579.
28. Levisohn L, Cronin-Golomb A, Schmahann JD. Neuropsychological consequences of cerebellar tumour resection in children. Cerebellar cognitive affective syndrome in a paediatric population. Brain 2000; 123: 1041-1050.
29. Allen G, Muller RA, Courchesne E. Cerebellar function in Autism: Functional Magnetic Resonance Image activation during a simple motor task. Biol Psychiatry 2004; 56: 269-278.
30. Critchley HD, Daly E, Bullmore ET, Williams SC, Van Amelsvoort T, Robertson DM, et al. The functional neuroanatomy of social behaviour. Changes in cerebral blood flow when people with autistic disorder process facial expressions. Brain 2000; 1: 2203-2212.
31. Grelotti DJ, Gauthier I, Schultz RT. Social interest and the development of cortical face specialization: what autism teaches us about face processing. Dev Psychbiol 2002; 40: 213-225.
32. Burgess N, Maguire EA, O'Keefe J. The human hippocampus and spatial and episodic memory. Neuron 2002; 35: 625-641.
33. Richter-Levin G. The amygdala, the hippocampus, and emotional modulation of memory. Neuroscientist 2004; 10: 31-39.
34. Rizzolatti G, Fabbri-Destro M. Mirror neurons: from discovery to autism. Exp Brain Res. 2010; 200: 223-237.
35. Simmons DR, Robertson AE, McKay LS, Toal E, McAleer P, Pollick FE. Vision in autism spectrum disorders. Vision Res. 2009; 49: 2705-2739.
36. Lind SE, Bowler DM. Recognition memory, self-other source memory, and theory-of-mind in children with autism spectrum disorder. J Autism Dev Disord. 2009; 39: 1231-1239.
37. Paul LK Brown WS, Adolphs R, Tyszka JM, Richards LJ, Mukherjee P, Sherr EH. Agenesis of the corpus callosum: genetic, developmental and functional aspects of connectivity. Nat Rev Neurosci 2007; 8: 287-299.
38. Keary CJ, Minshew NJ, Bansal R, Goradia D, Fedorov S, Keshaven MS, Hardan AY. Corpus callosum volume and neurocognition in autism. J Autism Dev Disord. 2009; 39: 839-841.
39. Idring S, Rai D, Dal H, Dalman C, Sturm H, Zander E, et al. Autism spectrum disorders in the Stockholm Youth Cohort: design, prevalence and validity. PLoS One 2012; 7: 241280.
40. Kopp S, Gillberg C. The Autism Spectrum Screening Questionnaire (ASSQ)-Revised Extended Version (ASSQ-REV) and instrument for better capturing the autism phenotype in girls? A preliminary study involving 191 clinical cases and community controls. Res Dev Disabil 2011; 32: 2875-2888.
41. Lai MC, Lombardo MV, Suckling J, Ruigrok AN, Chakrabarti B, Ecker C, et al. Biological sex affects the neurobiology of autism. Brain 2013; 136:2799-815.
42. Craig MC, Zaman SH, Daly EM, Cutter WJ, Robertson DMW, Hallahan B et al., Women with autistic-spectrum disorder: magnetic resonance imaging study of brain anatomy. Br J Psychiatry 2007; 191:224-228.
43. Greimel E, Schulte-Rüther M, Kircher T, Kamp-Becker I, Remschmidt H, Fink GR, Herpertz-Dahlmann B, Konrad K: Neural mechanisms of empathy in adolescents with autism spectrum disorder and their fathers. NeuroImage 2010, 49: 1055-1065.
44. Koshino H, Kana RK, Keller TA, Cherkassky VL, Minshew NJ, Just MA: fMRI investigation of working memory for faces in autism: visual coding and underconnectivity with frontal areas. Cereb Cortex 2008, 18: 289-300.
45. Wang AT, Lee SS, Sigman M, Dapretto M: Reading affect in the face and voice: neural correlates of interpreting communicative intent in children and adolescents with autism spectrum disorders.

Arch Gen Psychiatry 2007, 64: 698-708.
46. Just MA, Cherkassky VL, Keller TA, Minshew MJ. Cortical activation and synchronization during sentence comprehension in high- functioning autism: evidence of underconnectivity. Brain 2004; 127: 1811-1821.
47. Sahyoun CP, Belliveau JW, Soulières I, Schwartz S, Mody M. Neuroimaging of the functional and structural networks underlying visuospatial vs. linguistic reasoning in high-functioning autism. Neuropsychologia 2010; 48: 86-95.
48. Ebish SJ, Gallese V, Willems RM, Mantini D, Groen WB, Romani GL, et al. Altered intrinsic functional connectivity of anterior and posterior insula regions in high-functioning participants with autism spectrum disorder. Hum Brain Mapp 2011; 32: 1013-1028.
49. Solomon M, Ozonoff SJ, Ursu S, Ravizza S, Cummings N, Ly S, et al. The neural substrates of cognitive control deficits in autism spectrum disorders. Neuropsychologia 2009; 47: 2515-2526.
50. Deeley Q, Daly EM, Surguladze S, Page L, Toal F, Robertson D, Curran S, et al. An event related functional magnetic resonance imaging study of facial emotion processing in Asperger syndrome. Biol Psychiatry. 2007; 62: 207-217.
51. Pelphrey KA, Morris JP, McCarthy G, Labar KS. Perception of dynamic changes in facial affect and identity in autism. Soc Cogn Affect Neurosci 2007; 2: 140-149.
52. Daly EM, Deeley Q, Ecker C, Craig M, Hallahan B, Murphy C, et al. Serotonin and the neural processing of facial emotions in adults with autism: An fMRI study using acute tryptophan depletion. Arch Gen Psychiatry 2012; 69: 1003-1013.
53. Anagnostou E, Taylor MJ. Review of neuroimaging in autism spectrum disorders: what have we learned and where we go from here. Mol Autism 2011; 2:4.
54. Fletcher PT Whitaker RT, Tao R, DuBray MB, Froehlich A, Ravichandan C, et al. Microstructural connectivity of the arcuate fasciculus in adolescents with high-functioning autism. Neuroimage 2010; 51: 1117-1125.
55. Barnea-Goraly N, Lotspeich LJ, Reiss AL: Similar white matter aberrations in children with autism and their unaffected siblings: a diffusion tensor imaging study using tract-based spatial statistics. Arch Gen Psychiatry 2010, 67:1052-1060.
56. Sivaswamy L, Kumar A, Rajan D, Behen M, Muzik O, Chugani D, Chugani H. A. Diffusion Tensor Imaging study of the cerebellar pathways in children with Autism Spectrum Disorder. J Child Neurol 2010, 25:1223-1231.
57. Cheung C, Chua SE, Cheung V, Khong PL, Tai KS, Wong TK, et al. White matter fractional anisotropy differences and correlates of diagnostic symptoms in autism. J Child Psychol Psychiatry; 50: 1102-1112.
58. Lee JE, Bigler ED, Alexander AL, Lazar M, DuBray MB, Chung MK, et al. Diffusion tensor imaging of white matter in the superior temporal gyrus and temporal stem in autism. Neurosci Lett 2007; 434: 127-32.
59. Ben Bashat D, Kronfeld-Duenias V, Zachor DA, Ekstein PM, Hendler T, Tarrasch R, et al. Accelerated maturation of white matter in young children with autism: a high b value DWI study. Neuroimage 2007; 37: 40-47.
60. Cheng Y, Chou KH, Chen IY, Fan YT, Decety J, Lin CP. Atypical development of white matter microstructure in adolescents with autism spectrum disorders. Neuroimage 2010; 50: 873-882.
61. O'Brien F, Page L, O'Gorman RL, Bolton P, Sharma A, Baird G, et al. Maturation of limbic regions in Asperger syndrome: a preliminary study using proton magnetic resonance spectroscopy and structural magnetic resonance imaging. Psychiatry Res Neuroimaging 2010; 184: 77-85.
62. Fujii E, Mori K, Miyazaki M, Hashimoto T, Harada M, Kagami S. Function of the frontal lobe in autistic individuals: a proton magnetic resonance spectroscopic study. J Med Invest 2010; 57: 35-44.
63. Bernardi S, Anagnostou E, Shen J Kolevzon A, Buxbaum JD, Hollander E, Hof PR, Fan J. In vivo 1-H-magnetic resonance spectroscopy study of the attentional network in autism. Brain Res 2011; 1380: 198-205.