Review Article

iMedPub Journals
www.imedpub.com

Dual Diagnosis :Open Access
ISSN 2472-5048

2020
Vol.5 No.1:2

DOI: 10.36648/2472-5043.5.1.2

Emphasizing on the Neurobiological Basis of Autism Spectrum Disorder: A Closer Look to a Different Brain

Maria Sofologi[1*], Eva Markou[2], Georgios A Kougioumtzis[3], Afroditi Kamari[4], Antonis Theofilidis[1] and Elina Bonti[5]

[1]Department of Psychiatry, University General Hospital of Thessaloniki AHEPA, Thessaloniki, Greece

[2]Department of Special Education, European University of Cypru, Egkomi, Cyprus

[3]Department of Turkish Studies and Modern Asian Studies, University of Athens School of Economic and Political Sciences, Athens, Greece

[4]Department of Bioethincs, SDimokritus University of Thrake, Xanthi, Greece

[5]Medical School, 1st Psychiatry Clinic, Aristotle University of Thessaloniki, Papageorgiou Hospital, Pavlos Melas 564 29, Greece

[*]**Corresponding author:** Maria Sofologi, Department of Psychiatry, University General Hospital of Thessaloniki AHEPA, Thessaloniki, Greece, E-mail: msofolo@yahoo.gr

Received date: January 30, 2020; **Accepted date:** February 17, 2020; **Published date:** February 24, 2020

Citation: Sofologi M, Markou E, Kougioumtzis GA, Kamari A, Theofilidis A, et al. (2020) Emphasizing on the Neurobiological Basis of Autism Spectrum Disorder: A Closer look to a Different Brain. Dual Diagn Open Acc Vol.5 No.1:2.

Abstract

Autistic Spectrum Disorders (ASD) is an umbrella term that describes a range of common neurodevelopmental disorders affecting approximately 1% of the population. ASD are characterized by multilateral shortages, such as difficulties in communication and social interaction, repetitive, stereotypical behaviors and a limited scope of interests, mobility problems and disorders of language development, as well. These deficits do not follow the norm; on the contrary, great differentiation in their profiles and severity is observed between different people. ASD have, to a great degree, a hereditary, genetic basis however up to a decade ago, the researchers focusing on their neurobiological background were few. The present review study is an attempt to shed light on the neurobiological pathway of Autism Spectrum Disorder.

Keywords: Autism spectrum disorder; Brain networks; Connectivity

Introduction

The last decade, there has been an intense research emphasizing on the polymorphous patterns of neurobiological mutations present in ASD. The findings pertain to such diverse differences compared to the neurotypical population in the neural, structural-functional, molecular, endocrine, electrophysiological and genetic levels and also in the connectivity and neurotransmission levels, that many investigators are led to a hypothesis of a radically different brain organization [1-3]. Based on the neurobiological findings, we are now able to explain about 10%-20% of ASD cases. In the following sections, detailed descriptions of the neurobiological differences of individuals with ASD are given compared to the neurotypical population at various levels and their association with the cognitive and behavioral profile of the observed deficits.

One of the first confirmed findings is regarding the non-normotypical brain over-development of people with ASD during childhood. The majority of studies were conducted on infants or children aged one year or over, for the duration of their childhood. Thus, researchers hypothesize that this over-development might be related to the first clinical symptoms of autism, cognitive and behavioral, observed at this age [4]. For example, in a recent study, Hazlett et al. examined the growth rate of cerebral volume (white and gray matter) and cortical thickness in children aged two years [5]. They also performed a repeat measurement two years later. The results showed that children with ASD had approximately 9% greater gray and white matter volume compared to the control group at both time points, while they did not differ in cortical thickness. Despite this difference, the rate of brain development was the same between the groups, as was indicated by the lack of intergroup differences in cerebral volume between the two time points, which according to the researchers is due to an increased growth rate before the age of two. The study by Schumann et al. resulted in similar findings, the difference being that the size and growth rate of gray matter were greater in the anterior areas of the brain (frontal, temporal, parietal) compared to the posterior areas [6]. Moreover, non-normotypical over-development was mainly observed in the temporal regions. In addition, in a rare recent study, Calderoni et al. investigated the brain volume of various structures in a group consisting entirely of girls with ASD (2 to 7 years old) and a matched control group [7]. The findings showed a 5% greater overall size of intracranial structures in girls with ASD compared to the control group, and a particularly noticeable enlargement in gray matter in the superior frontal gyrus bilaterally and in the right temporo-

parietal joint. Yet, it is worth noting that there are also a percentage of researchers who did not confirm greater cerebral size in persons with ASD [8].

However, developmental studies show that brain development does not follow the same pattern during adolescence and adulthood, when there seems to be greater impairment of the brain tissue in people with ASD than in the average population estimated the differences in the thickness of the cerebral cortex between adolescents with high-functioning autism and a matched control group. The findings showed that people with autism had significantly less cerebral cortical thickness compared to the control group, mainly in the left temporal and parietal areas (e.g. in the superior temporal sulcus and the posterior temporal, upper parietal and supramarginal gyrus). In addition, it was shown that individuals with autism had a significantly higher rate of cortical thinning in the left fusiform/posterior temporal cortical area as they age compared to the control group. These findings are supported by earlier studies, as well, which indicated greater cortical atrophy, reduced amygdala volume and reduced volume of the frontal cortex in adolescents and adults with autism compared to individuals with neurotypical development [9-15].

We are not yet sure regarding the significance of these findings and the different age patterns of brain development in individuals with ASD. In any case, it seems they are not directly relevant to functionality during childhood or adult life [16]. For example, Hutsler and Zhang observed that adolescents and adults with ASD had significantly higher density of dendritic spines than persons of normotypical development, and although cerebral developmental disorders are often associated with the existence of fewer dendritic spines, none of the individuals with ASD had a smaller number than any person in the control group[17]. These differences were mainly found in the second superficial stratum of the temporal, frontal, and parietal areas [18].

Amygdala

The amygdala constitutes a brain structure made up of 13 nuclei and is located under the hook of the temporal lobe, at the anterior end of the hippocampal formation and the lower horn of the lateral abdomen. It is part of the limbic system, connected to many other areas of the brain, such as the frontal cortex, the hippocampus, the cingulate cortex and the hypothalamus, and is involved in higher processes, such as the regulation of emotion and stress response, memory and learning, in particular of emotionally charged stimuli, and social interaction; these processes are often disturbed in ASD [19-25].

Indeed, many studies prove structural differences of ASD individuals in the amygdala, mainly increased structural size and higher growth rate, using current neuro-imaging methods [26,27]. For example, Schumann et al. measured, by magnetic resonance imaging, the size of the amygdale in 89 infants (boys and girls) aged 1 to 5 years and found that infants who were later diagnosed with autism had a larger amygdala size bilaterally compared to neurotypically developing children [28]. Additionally, the same researchers found that the size of the amygdala was proportional to the severity of the social and communication deficits that these infants exhibited. It is worth noting that the observed differences in the size of the amygdala were more prominent in the girls involved in the study, an indication of the effect of gender on brain organization. Similar findings are reported in the study by Nordahl et al. as well, who estimated the total volume of the cerebral cortex and of the amygdala at two time points (at examination and 1 year after), in 85 boys with ASD and a matched control group[29]. The results showed that at both time points, infants with ASD had higher cortical and amygdala volume compared to the control group. Indeed, it was shown that the magnitude of the difference was greater in the second measurement, only for the amygdala, a fact which shows that in people with ASD, not only the volume is greater but also the growth rate of the structure. Similarly, Mosconi et al. examined the association between the volume of the amygdala and the expression of specific behaviors in children with ASD, at two time points (2 and 4 years) [30]. The results indicated that in both measurements, children with ASD had a larger amygdala bilaterally in relation to the control group. Moreover, although there appeared to be a large increase in the volume of the structure between the two time points, there was no difference between children with ASD and a control group, contrary to the findings of Nordahl et al. [29]. Lastly, a study was conducted that emphasized the significance of ensuring homogeneity of diagnoses in the experimental group when such studies are conducted [31]. More specifically, the researchers showed that children with ASD and fragile X (chromosome) syndrome had a significantly larger volume of caudate nucleus and a smaller amygdala compared to children with neurotypical development. Rather, children with ASD without the syndrome (e.g. idiopathic autism) showed moderate enlargement of the caudate nucleus, but notably enlarged amygdala compared to the control group.

Another inadequacy often observed in individuals with ASD is problematic facial recognition capability, an inadequacy which has been hypothesized to be due to dysfunction of the amygdala [32]. The amygdala is over-activated by novel stimuli and its response time is decreased through the person ' s repeated exposure to the same stimulus, a phenomenon called familiarity. Recent studies show that in people with ASD there is a different standard of functioning. Firstly, the response time of the amygdala to new stimuli (e.g., an unknown person/face) is slower compared with that in individuals of normotypical development and secondly, this time does not tend to decrease through repeated exposure to the same person/face as opposed to the average population [31]. Indeed, in a recent study by Kleinhans et al. it was found that amygdala activation in people with ASD tended to increase with repeated exposure to negatively emotionally charged individuals [33]. Moreover, while in normotypical development subjects the right lateral fusiform gyrus tends to present a similar activation pattern to that of the amygdala, i.e. impaired response with repeated exposure to the same stimulus, no functional differences of the area were seen in subjects with ASD although activation of the amygdala increased [34]. According to the researchers, this finding was likely due to altered connectivity between the two regions.

Hippocampus

Similar structural-functional differences have been reported for the hippocampal region. For example, research by Dager and colleagues unveiled a distinctly different form in the structure of the hippocampus in children with ASD [35]. In fact, these differences seemed to follow a different pattern in autism cases from the cases of diffuse developmental disorder not otherwise specified.

Frontal Cortex

Similarly, increased cortical volume in people with ASD has also been observed in frontal sites. For example, in their cross-sectional study, Carper and colleagues report a model of over-increase in the cerebrum of children with ASD, where the frontal sites (e.g. frontal cortex) exhibited notably larger volume compared with posterior sites (e.g., occipital lobe). In a recent study, Courchesne and colleagues posthumously examined the prefrontal cortex of 7 children with ASD compared to 6 children of normotypical development aged 2 to 16 years [36]. The study findings revealed that subjects with ASD had 67% more neuronal cells in total, of which 79% more in the lateral posterior prefrontal cortex and 29% more in the medial prefrontal cortex compared to the control group [10]. Also, the two groups differed in the overall cerebral growth rate with age, as it was found that people with ASD exhibited differences by an average of 17.6% with age, contrary to the control group where differences were only by 0.2% on average.

Temporal Cortex

Delay in language development constitutes one of the first predictive factors of ASD in childhood [37]. Non-normotypical linguistic development, according to many researchers, is interpreted based on structural-functional differences in temporal areas of the brain. For example, Redcay and Courchesne indicated that children with ASD, aged 2-3 years, had reduced connectivity to parts of the temporal cortex during sleep compared to a matched control group [38]. A recent study found differences in laterality of temporal lobe functions in children with ASD [39]. The study researchers measured cerebral activity while reading a fairy tale and found that children with ASD had an inadequate response of the left hemisphere to sonic speech prompts, while presenting a non-normotypical response of the right temporal lobe.

Finally, as mentioned in a previous section, the difficulty autistic people have in recognizing faces is typical, a function seated on the temporal lobe and, specifically, on the fusiform gyrus. A study by Van Kooten and colleagues indicated that there are mutations in the fusiform gyrus in the brains of autistic persons, and, specifically, a lower density and number of neurons and average volume of neuronal cell pericarps [40]. No similar differences were noted for the other regions examined, such as the primordial visual cortex and the total cerebral cortex.

Electrophysiological Function

The ability to recognize faces in ASD was also investigated using electrophysiological measurements. For example, one study examined the electrophysiological function in 10-month-old infants at high risk of developing ASD, as their sibling had the disorder [41]. The researchers used Induced Dynamics and estimated four values, i.e. P100, N290, P400 and Nc. The results showed that the control group reacted more quickly to faces rather than objects, as was estimated by the P400 index, a difference that was not seen in the experimental group (infants at a high risk of developing ASD). In contrast, a faster response of infants with ASD to objects rather than faces was observed (N290). This response to objects was significantly greater compared to the control group, as was revealed by the N290 and P400 dynamics. Similar deficits were also noted in the study by Luyster, Wagner et al., who examined the electrophysiological activity of the brain in infants exposed to images of known and unknown faces [42]. The results suggested that infants with normotypical development used more attention resources (Nc) when looking at an unknown person compared to a known one, a difference that was not confirmed in the control group. In a further study, saccadic eye movements were examined in infants with ASD and in children with normotypical development, who had a first measurement at two years and a repeat two years later. The researchers concluded that children with ASD had a different pattern of ocular movements when scanning a face in relation to children with normotypical development. These differences became more pronounced after two years. Moreover, children with ASD tended to avoid looking at the image of the face at 4 years of age [43].

Connectivity

Increasingly, findings indicate that cerebral function consists of networks of sites that interact and cooperate. Recent studies show that communication between areas of the brain is probably disarranged in people with ASD. For example, some theorists contend that there are communication difficulties between frontal and posterior cerebral structures [44,45].

In persons with ASD, scarcity in social interaction is typical, such as inadequate visual contact, lack of empathy, and inability to understand figures of speech, humor etc. Current experts claim that these deficits might be based on wider functional differences in people with ASD. For example, Hoffmann et al. found decreased connectivity between the left temporal voice processing area and the upper and middle frontal gyrus [46]. The same researchers revealed that connectivity mutations were proportional to the severity of ASD symptoms and affected sites that play a defining role in perceiving and interpreting social stimuli. Specifically, the connectivity between the left temporal area for voice processing and the limbic system, the anterior cingulate gyrus and the middle frontal gyrus, and the connectivity between the right temporal area for voice processing and the frontal lobe, the anterior cingulated cortex, the limbic system and the caudate nucleus declined as the severity of autism symptoms ascended.

Interhemispheric Function

In a study by Dinstein and colleagues, distorted synchronism o f the spontaneous cortical activity was observed in infants with ASD, compared to infants of normotypical development. Indeed, weak connectivity between the two hemispheres was detected mainly in the posterior frontal gyrus and the superior temporal gyrus, areas linked to speech comprehension and production [47]. The strength of the connectivity of the two hemispheres was inversely proportional to the severity of the ASD symptoms. Furthermore, research by Ecker and colleagues demonstrated that the left hemisphere is the one that exhibits more distinct patterns of structural-functional alterations in individuals with ASD, thus it is more sensitive to the differentiation of these subjects from the neurotypical population [48].

Mitochondrial Abnormalities

Research shows that up to 20% of autism cases are associated with mitochondrial abnormalities. For example, Goh et al. found peripheral markers of mitochondrial abnormalities in people with ASD, such as elevated levels of lactic acid, which suggests metabolic dysfunction, mainly in the locality of the cingulate gyrus, a structure involved in many higher processes, such as the regulation of emotion, cogitation and behavior regulation [49].

Endocrine Differences

Several studies demonstrate that the neurobiological differences of people with ASD are also detected at the endocrine level. A recent study by Spratt et al. in 20 children with ASD and 28 children without a history of neurodevelopmental disorders uncovered a dysfunction of the stress response axis in subjects with ASD [50]. The researchers analysed the concentration of cortisol in the sputum of subjects during rest, during exposure to a new environment and during exposure to stress stimuli (drawing blood). At rest, the groups had comparable cortisol levels. The groups showed high levels of cortisol 20 minutes after blood sampling with the experimental group having significantly higher anxiety levels. Also, 40 minutes after drawing blood, the cortisol levels in subjects with ASD had not returned to resting state levels, while they were completely reset in the control group. Gender had no effect on the results. These findings suggest that people with ASD are prone to manifesting enhanced sensitivity of the Hypothalamic-Pituitary-Adrenal axis to stress, while feedback of the axis is delayed. A large, contemporary study by Baron-Cohen et al. yielded comparable findings [51]. The researchers investigated samples of amniotic fluid from all males born between 1993 and 1999 in Denmark and later diagnosed with ASD and compared them with amniotic samples of individuals with normotypical development. In the samples, the steroid hormone levels were measured, and among them the cortisol levels, and were found to be significantly increased in individuals with ASD compared to subjects with normotypical development. This study was the first large-scale study that unveiled the elevated prenatal activity of steroid hormones in individuals with ASD.

There are comparable findings indicating dysfunction regardin g melatonin. Approximately 44%-83% of people with ASD encounter sleep quality disruption, such as frequent nocturnal awakenings and longer sleep onset latency, alterations that can worsen the behavioral symptoms of autism. Research shows that, indeed, melatonin levels are decreased in 65% of persons with ASD due to dysfunction of the enzyme acetylserotonin O-methyltransferase (ASMT). An ASMT polymorphism causes up to 50% drop in melatonin concentration [52-58].

Conclusion

Furthermore, a study of subjects with ASD from Italy, the United Kingdom and Finland showed that these individuals have a high percentage of several types of ASMT polymorphisms. In addition, a study by Rossignol and Frye revealed that people on melatonin medication had up to 80% improvement in the quality of their sleep, with longer overall sleep duration and easier onset. Also, a recent study by Carson and colleagues found that some dysfunction of vasopressin may account for social inefficiencies in children with ASD. The researchers compared three groups (children with ASD, their siblings without ASD, and one neurotypical development group) as to their blood vasopressin levels and assessed their social functionality by weighted tests. The results showed that although the groups did not directly differ from each other, blood vasopressin levels were positively correlated with subjects' performance in the “Theory of Mind” and “Social Intelligence” tests. Finally, ASD have been associated with elevated levels of growth hormone (GH) and of insulin-like growth factor (IGF-1/) in cerebrospinal fluid. Specifically, Mills and colleagues looked into the role of GH and IGF-1 in boys with ASD and observed that these boys had significantly bigger head perimeter, increased weight and body mass index, without diverging from a matched control group in terms of height.

References

1. Allely CS, Gillberg C, Wilson P (2014) Neurobiological abnormalities in the first few years of life in individuals later diagnosed with autism spectrum disorder: A review of recent data. Behavioural Neurology 2014: 1-20.
2. Rippon G, Brock J, Brown C, Boucher J (2007) Disordered connectivity in the autistic brain: Challenges for the ‘new psychophysiology’. 63: 164-172.
3. Geschwind D. (2007) Autism: searching for coherence. 62: 949-950.
4. Pierce K, Glatt SJ, Liptak GS, McIntyre LL (2009) The power and promise of identifying autism early: Insights from the search for clinical and biological markers. Ann Clin Psychiatry 21: 132-147.
5. Hazlett HC, Poe MD, Lightbody AA, Styner M, MacFall JR, et al. (2012) Trajectories of early brain volume development in fragile X syndrome and autism. 51: 921-933.
6. Schumann CM, Bloss CS, Barnes CC, Wideman GM, Carper RA, et al. (2010) Longitudinal magnetic resonance imaging study of cortical development through early childhood in autism. 30: 4419-4427.

7. Calderoni S, Retico A, Biagi L, Tancredi R, Muratori F, et al. (2012) Female children with autism spectrum disorder: An insight from mass-univariate and pattern classification analyses. 59: 1013-1022.
8. Hazlett HC, Gu H, McKinstry RC, Shaw DW, Botteron KN, et al. (2012) Brain volume findings in 6-month-old infants at high familial risk for autism. 169: 601-608.
9. Aylward EH, Minshew NJ, Field K, Sparks BF, Singh N (2002) Effects of age on brain volume and head circumference in autism. Neurology 59: 175-183.
10. Courchesne E, Mouton PR, Calhoun ME, Semendeferi K, Ahrens-Barbeau C et al. (2011) Neuron number and size in prefrontal cortex of children with autism. JAMA 306: 2001-2010.
11. Wallace GL, Dankner N, Kenworthy L, Giedd JN, Martin A (2010) Age-related temporal and parietal cortical thinning in autism spectrum disorders. Brain 133: 3745-3754.
12. Hadjikhani N, Joseph RM, Snyder J, Tager-Flusberg H (2006) Anatomical differences in the mirror neuron system and social cognition network in autism. Cerebral Cortex 16: 1276-1282.
13. Pierce K, Haist F, Sedaghat F, Courchesne E (2004) The brain response to personally familiar faces in autism: Findings of fusiform activity and beyond. Brain 127: 2703-2716.
14. Kosaka H, Omori M, Munesue T, Ishitobi M, Matsumura Y, et al. (2010) Smaller insula and inferior frontal volumes in young adults with pervasive developmental disorders. Neuroimage 50: 1357-1363.
15. WoodburySmith M, Scherer SW (2018) Progress in the genetics of autism spectrum disorder. Dev Med Child Neurol 60: 445-451.
16. Zeegers M, Pol HH, Durston S, Nederveen H, Schnack H, van Daalen E, et al. (2009) No differences in MR-based volumetry between 2-and 7-year-old children with autism spectrum disorder and developmental delay. Brain Dev 31: 725-730.
17. Hutsler JJ, Zhang H (2010) Increased dendritic spine densities on cortical projection neurons in autism spectrum disorders. Brain Research 1309: 83-94.
18. Nunes AS, Peatfield N, Vakorin V, Doesburg SM (2019) Idiosyncratic organization of cortical networks in autism spectrum disorder. Neuroimage 190: 182-190.
19. Etkin A, Egner T, Peraza DM, Kandel ER, Hirsch J (2006) Resolving emotional conflict: A role for the rostral anterior cingulate cortex in modulating activity in the amygdala. Neuron 51: 871-882.
20. Kim JJ, Lee HJ, Han JS, Packard MG (2001) Amygdala is critical for stress-induced modulation of hippocampal long-term potentiation and learning. J Neurosci 21: 5222-5228.
21. Baron-Cohen S, Auyeung B, Nørgaard-Pedersen B, Hougaard DM, Abdallah MW, et l. (2015) Elevated fetal steroidogenic activity in autism. Mol Psychiatry 20: 369-376.
22. Davis M (1992) The role of the amygdala in fear and anxiety. Annu Rev Ne 15: 353-375.
23. Price JL, Russchen FT, Amaral DG (1987) The limbic region. II. The amygdaloid complex. Handbook of chemical neuroanatomy 5: 279-388.
24. Love JR, Carr JE, LeBlanc LA (2009) Functional assessment of problem behavior in children with autism spectrum disorders: A summary of 32 outpatient cases. J Autism Dev Disord 39: 363-372.
25. Schultz RT (2005) Developmental deficits in social perception in autism: The role of the amygdala and fusiform face area. Int J Dev Neurosci 23: 125-141.
26. Schumann CM, Hamstra J, Goodlin-Jones BL, Lotspeich LJ, Kwon H, et al. (2004) The amygdala is enlarged in children but not adolescents with autism; the hippocampus is enlarged at all ages. J Neurosci 24: 6392–6401.
27. Sparks BF, Friedman SD, Shaw DW, Aylward EH, Echelard D, et al. (2002) Brain structural abnormalities in young children with autism spectrum disorder. Neurology 59: 184–192.
28. Schumann CM, Barnes CC, Lord C, Courchesne E (2009) Amygdala enlargement in toddlers with autism related to severity of social and communication impairments. Biol Psychiatry 66: 942-949.
29. Nordahl CW, Scholz R, Yang X, Buonocore MH, Simon T, et al. (2012) Increased rate of amygdala growth in children aged 2 to 4 years with autism spectrum disorders: A longitudinal study. Arch Gen Psychiatry 69: 53-61.
30. Mosconi MW, Cody-Hazlett H, Poe MD, Gerig G, Gimpel-Smith R, et al. (2009) Longitudinal study of amygdala volume and joint attention in 2-to 4-year-old children with autism. 66: 509-516.
31. Hazlett HC, Poe MD, Lightbody AA, Gerig G, MacFall JR, et al. (2009) Teasing apart the heterogeneity of autism: Same behavior, different brains in toddlers with fragile X syndrome and autism. J Neurodev Disord 1: 81.
32. Webb SJ, Jones EJ, Merkle K, Namkung J, Toth K, et al. (2010) Toddlers with elevated autism symptoms show slowed habituation to faces. 16: 255-278.
33. Kleinhans NM, Richards T, Greenson J, Dawson G, Aylward E (2016) Altered dynamics of the fMRI response to faces in individuals with autism. 46: 232-241.
34. Ishai A, Pessoa L, Bikle PC, Ungerleider LG (2004) Repetition suppression of faces is modulated by emotion. PNAS 101: 9827–9832.
35. Dager SR, Wang L, Friedman SD, Shaw DW, Constantino JN, et al. (2007) Shape mapping of the hippocampus in young children with autism spectrum disorder. AJNR 28: 672-677.
36. Courchesne E, Karns CM, Davis HR, Ziccardi R, Carper RA, et al. (2001) Unusual brain growth patterns in early life in patients with autistic disorder an MRI study. Neurology 57: 245-254.
37. De Giacomo A, Fombonne E (1998) Parental recognition of developmental abnormalities in autism. Eur Child Adol Psy 7: 131-136.
38. Redcay E, Courchesne E (2008) Deviant functional magnetic resonance imaging patterns of brain activity to speech in 2–3-year-old children with autism spectrum disorder. Biol Psychiatry 64:589-598.
39. Eyler LT, Pierce K, Courchesne E (2012) A failure of left temporal cortex to specialize for language is an early emerging and fundamental property of autism. Brain 135: 949-960.
40. van Kooten IA, Palmen SJ, von Cappeln P, Steinbusch HW, Korr H, et al. (2008) Neurons in the fusiform gyrus are fewer and smaller in autism. Brain 131: 987-999.
41. McCleery JP, Akshoomoff N, Dobkins KR, Carver LJ (2009) A typical face versus object processing and hemispheric asymmetries in 10-month-old infants at risk for autism. Biol Psychiatry 66: 950-957.
42. Luyster RJ, Wagner JB, Vogel-Farley V, Tager-Flusberg H, Nelson III CA (2011) Neural correlates of familiar and unfamiliar face

processing in infants at risk for autism spectrum disorders. Brain Topogr 24: 220-228.

43. Chawarska K, Shic F (2009) Looking but not seeing: Atypical visual scanning and recognition of faces in 2 and 4-year-old children with autism spectrum disorder. 39: 1663-1672.

44. Just MA, Keller TA, Malave VL, Kana RK, Varma, S (2012) Autism as a neural systems disorder: A theory of frontal-posterior underconnectivity. 36: 1292-1313.

45. Just MA, Cherkassky VL, Keller TA, Minshew NJ (2004) Cortical activation and synchronization during sentence comprehension in high-functioning autism: Evidence of underconnectivity. Brain 127: 1811-1821.

46. Hoffmann E, Brück C, Kreifelts B, Ethofer T, Wildgruber D (2016) Reduced functional connectivity to the frontal cortex during processing of social cues in autism spectrum disorder. 1: 11.

47. Dinstein I, Pierce K, Eyler L, Solso S, Malach R, et al. (2011) Disrupted neural synchronization in toddlers with autism. Neuron 70: 1218-1225.

48. Ecker C, Marquand A, Mourão-Miranda J, Johnston P, Daly EM, et al. (2010) Describing the brain in autism in five dimensions-magnetic resonance imaging-assisted diagnosis of autism spectrum disorder using a multiparameter classification approach. 30: 10612-10623.

49. Goh S, Dong Z, Zhang Y, DiMauro S, Peterson BS (2014) Brain imaging evidence that mitochondrial dysfunction is a neurobiological subtype of Autism Spectrum Disorder. JAMA Psychiatry 71: 665.

50. Spratt EG, Nicholas JS, Brady KT, Carpenter LA, Hatcher CR et al. (2012) Enhanced cortisol response to stress in children in autism. 42:75-81.

51. Baron-Cohen S, Auyeung B, Nørgaard-Pedersen B, Hougaard DM, Abdallah MW, et al. (2015) Elevated fetal steroidogenic activity in autism. Mol Psychiatry 20: 369-376.

52. Johnson KP, Malow BA (2008) Sleep in children with autism spectrum disorders. 10: 350-359.

53. Limoges É, Mottron L, Bolduc C, Berthiaume C, Godbout R (2005) Atypical sleep architecture and the autism phenotype. Brain 128: 1049-1061.

54. Melke J, Botros HG, Chaste P, Betancur C, Nygren G, et al. (2008) Abnormal melatonin synthesis in autism spectrum disorders. 13: 90-98.

55. Jonsson L, Ljunggren E, Bremer A, Pedersen C, Landén M, et al. (2010) Mutation screening of melatonin-related genes in patients with autism spectrum disorders. 3: 10.

56. Rossignol DA, Frye RE (2011) Melatonin in autism spectrum disorders: A systematic review and metaanalysis. 53: 783-792.

57. Carson DS, Garner JP, Hyde SA, Libove RA, Berquist SW, et al. (2015) Arginine vasopressin is a blood-based biomarker of social functioning in children with autism. PloS One 10: 7.

58. Mills JL, Hediger ML, Molloy CA, Chrousos GP, Manning Courtney P, et al. (2007) Elevated levels of growth-related hormones in autism and autism spectrum disorder. Clin Endocrinol 67: 230-237.