2012 INTERAGENCY AUTISM COORDINATING COMMITTEE STRATEGIC PLAN UPDATE: QUESTION 2 HOW CAN I UNDERSTAND WHAT IS HAPPENING?

WHAT IS NEW IN THIS RESEARCH AREA, AND WHAT HAVE WE LEARNED IN THE PAST TWO YEARS?

In 2011 and 2012, significant progress has been made in understanding the underlying biology of ASD. This includes new observations about differences in neural connectivity in the brains of those with ASD, the discovery of molecular mechanisms that might cause autism symptoms, and insights from some of the conditions and disorders that co-occur with autism.

Brain Imaging

In the past two years there have been more than 225 research publications that have used neuroimaging of brain structure or connectivity to look for differences in autism. In response to the urgent need for sensitive and specific biomarkers for the diagnosis of ASD, many research groups have been studying patterns of brain development, including prospective longitudinal studies of infant siblings of children with ASD. Some traction has been gained by using diffusion weighted imaging (DWI, an imaging technique in which the diffusion of water molecules is mapped in order to reveal the underlying structure of the brain) to study white matter pathways. Research using this technique found atypical development of white matter pathways in high-risk infants (infants who had an older sibling with ASD) who later developed autistic symptoms (Weinstein et al., 2011). Abnormal white matter architecture was also found in three year old children with autism (Wolff et al., 2012).

Another recent trend is to use structural magnetic resonance imaging (structural MRI) to define neural phenotypes of autism. Several studies (e.g., Hoeft et al., 2011) have demonstrated that young boys with fragile X syndrome have different patterns of brain abnormalities than young boys with idiopathic autism. Other studies have shown that the accelerated brain growth associated with autism is observed mainly in young boys with regressive autism (Nordahl et al., 2011) and does not occur in girls with autism. Interestingly, enlarged brain size may be related to ethnicity, since macrocephaly (abnormally enlarged head) is not a common feature of autism in Israel (Davidovitch et al., 2011).

Over the past two years, an array of studies using functional magnetic resonance imaging (fMRI) and DWI has advanced understanding of the neural circuitry that is affected in ASD. These studies have most often highlighted differences in functional activation within specific brain regions known to be specialized for processing social information (e.g., social orienting, Greene et al., 2011; affective aspects of social processing, Gotts et al., 2012; gaze on emotional faces, Kliemann et al., 2012; attention, Redcay et al., 2012). Diffusion weighted imaging studies found disrupted pathways connecting language areas in children with autism (Lewis et al., 2012).

Neurophysiology

Investigating neural circuits in the brain may reveal distinctions that cannot be observed by behavioral approaches alone. For example, brain activity has potential as an early predictor of subsequent ASD diagnosis. Electroencephalography (EEG) is a technique in which electrical activity along the scalp is used to measure current flow in the brain. EEG responses to dynamic eye gaze shifts (viewing faces with eye gaze directed toward versus away from the infant) during the first year predicted different clinical outcomes at 36 months (Elsabbagh et al., 2012). This difference in brain activity was apparent despite similar patterns of gaze as measured by eye tracking. Atypical audiovisual speech integration in infants at-risk for autism has also been shown (Guiraud et al., 2012). As the field strives for earlier methods of detecting autistic development, these findings, together with the neuroimaging findings described above, offer hope for the possibility of non-invasive, brain-based screening methods that could detect differences prior to the emergence of ASD behavioral symptoms.

Molecular Basis and Phenotyping

Genetic studies continue to implicate dysfunction at the synapse—the junctions through which neurons transmit signals to each other—as part of the underlying biology of ASD. Of particular interest are the insights into the effects of gene mutations in animal models of syndromic autism, including FMRP (Fragile X Mental Retardation protein) in fragile X syndrome, MecP2 in Rett syndrome and TSC1/2 in tuberous sclerosis. Remarkably, these mouse studies support the hypothesis that many aspects of the ASD phenotype are reversible in both adults and infants; drugs influencing the mGluR5 receptor and the mTOR inhibitor, rapamycin, were found to be particularly effective (Tsai et al., 2012; Silverman et al., 2012; Auerbach, Osterweil & Bear, 2011). Rare mutations in genes that encode proteins forming large complexes at the synapse (Shank/ProSAP) are now known to be associated with autism. Deletions of these genes in mice were found to cause autism-like behaviors and alterations of synaptic function and glutamate neurotransmission (Schmeisser et al., 2012). Additionally, genetic deletions or duplications—called copy number variants (CNVs)—in other genes may interact with mutations in Shank to cause autism (Leblond et al., 2012).

As risk genes for ASD are identified at an increasing pace (see Question 3), the next step for brain imaging research is to determine how these risk genes impact the development of brain structure and function and contribute to the heterogeneity (diverse array of potential causes and presentation of symptoms) observed in people with ASD. For example, one fMRI study demonstrated that a common, functional ASD risk variant in the Met Receptor Tyrosine Kinase (MET) gene is an important regulator of key social brain circuitry in children and adolescents with and without ASD, with MET risk genotypes associated with atypical fMRI activation to emotional faces (Rudie et al., 2012). If validated, these findings highlight how different patterns in genetic variation may lead to an understanding of phenotypic heterogeneity in ASD and help to elucidate the key changes in neural circuitry.

A recent study examining gene expression in postmortem brains of individuals with autism showed a remarkable decrease in the typical variation seen between cortical regions in normal brains, a finding that suggests a simplification of cortical patterning in autism (Voineagu et al.,

2012). This study also uncovered patterns of neuronal gene expression in autism that paralleled and confirmed the role of genes known to be associated with autism risk. Surprisingly, the researchers also found a pattern of immune and glial cell gene expression in the autism brain that had not been identified in previous genetic studies, an observation that supports the view that brain immune system responses in autism are likely related to environmental events as well as genetic influences.

Immune System

Recent findings in experimental animals are critical for understanding the role of glial cells (non-neuronal cells that maintain homeostasis, form myelin, and provide support and protection for neurons in the brain and nervous system) and immune pathways in the development of autism and its underlying biology. Models of microglia (glial cells that form part of the immune system) and immune pathway function during brain development and neuroplasticity in experimental animals, which have suggested involvement of microglia in normal neurodevelopmental activities such as the "pruning" of synapses, are the strongest demonstration of a potential role for the immune system in ASD pathogenesis (Schafer et al., 2012; Stephan,Barres & Stevens, 2012).

The potential role of adaptive immunity, environmental factors (such as maternal infections), and autoimmunity in the pathogenesis of ASD has also been identified using animal models. In some recent studies, for example, maternal immune activation resulted in long-term adaptive immune system abnormalities, in the offspring of mice exposed to immune challenges during pregnancy (Hsiao et al., 2012; Braunschweig et al. 2012). Interestingly, behavioral abnormalities observed in this model were reduced by reversing cellular immune deficits with immunologically normal bone marrow (Hsiao & Patterson, 2012), which has implications for development of new interventions for ASD.

Although human studies of immune function in ASD have been limited, some observations support a potential link between immune dysfunction and autism. One study that evaluated cytokines and chemokine expression in neonatal blood spot samples in the Danish Newborn Screening Bank suggested that an underactive immune system was present in infants that developed autism (Abdallah et al., 2012).

Co-occurring Conditions

Over the past two years there has been increasing recognition of the substantial overlap between ASD and epilepsy. Past studies indicated that 10-20% of individuals with ASD have concurrent epilepsy. Within the past year, progress has been made on discovering the common roots of ASD and epilepsy, including identification of mutations in a gene coding for a metabolic enzyme (Novarino et al., 2012), and X-chromosome-linked mutations in a gene that produces proteins usually involved in cell adhesion (Marini et al., 2012).

Recent work has also reinforced the overlap between ASD and gastrointestinal disturbances. For instance, 24% of children with ASD enrolled in the Autism Speaks' Autism Treatment Network (ATN) were shown to have one or more chronic gastrointestinal problems, and these problems

were associated with higher rates of both anxiety and sensory over-responsivity (Mazurek et al., 2012).

Sleep dysfunction is also associated with ASD and often correlates with its severity. Children with ASD who sleep fewer hours per night demonstrate lower overall IQ, verbal skills, overall adaptive functioning, daily living skills, socialization skills, and motor development. Furthermore, children who wake during the night in addition to sleeping fewer hours exhibit more communication problems (Taylor, Schreck & Mulick, 2012). Children with autism spend reduced time in the rapid eye movement (REM) phase of sleep, which has been hypothesized to play a role in neuroplasticity—the brain's ability to reorganize itself by forming new neural connections—and brain development (Buckley et al., 2010). Naturally occurring levels of a major metabolite of melatonin—which signals sleep onset—has been documented to be low in adolescents and young adults with autism compared to age and gender-matched controls (Tordjman et al., 2012). These findings provide the groundwork for treatment trials of melatonin in ASD (see Question 4).

WHAT GAPS HAVE EMERGED IN THE PAST TWO YEARS?

Over the past two years several landmark efforts in biology have provided new tools and insights that may transform our understanding of ASD. While none of these efforts were focused on ASD, they provide unprecedented opportunities for future ASD research. The ENCODE project, for example, has demonstrated that the human genome is loaded with important biological signals beyond genes that code for proteins. While protein coding genes make up only 2% of the genome, new research revealed that about 80% of the genome is translated, resulting in some 20,000 non-coding RNA elements (Encode Consortium, 2012). Scientists working on ASD genetics have barely begun to explore these newly-discovered elements of the genome.

The Human Microbiome Project, which has mapped the microbial world of 18 different sites in the human body (Human Microbiome Consortium, 2012), has also provided important insights that have implications for many human conditions, including ASD. The results have altered thinking about what it means to be human, and the body is beginning to be viewed as more of a complex ecosystem in which human cells represent a paltry 10% of the population. But beyond the sheer numbers, this information brings new knowledge about the profound diversity of this ecosystem and striking individual differences. How these differences in the microbial world influence the development of brain, behavior, and neuroimmune function will be one of the great frontiers of clinical neuroscience in the next decade. In addition, the Human Connectome Project is providing the first detailed wiring diagram of the human brain, developing the tools for mapping the connections across distant regions of the cortex (Wedeen et al, 2012).

Turning to the basic issue of defining brain differences that contribute to autism, there continues to be a paucity of studies related to the cellular neuropathology of autism. The dearth of postmortem tissue has slowed research in every area addressed under this question. While this has been a challenge for many years, the loss of more than 50 brains after a freezer malfunction in June, 2012 has been an enormous setback. The loss represented about one third of the largest autism brain repository and will take years to replace (see Question 7).

In order to study the cellular and molecular underpinnings of autism, researchers also need appropriate cell culture models of neurons. In a landmark paper, investigators generated cortical neurons from induced pluripotent stem cells (iPSCs) derived from skin cells of two individuals with Timothy syndrome (Pasca et al., 2011). Interestingly, these neurons showed abnormalities in differentiation and neurotransmitter production that could be reversed by blocking the calcium channel known to be mutated in this monogenic, or single gene, cause of autism. iPSCs are promising both as a biological tool to uncover the pathophysiology of disease by creating relevant cell models and as a source of stem cells for cell-based therapeutic applications and drug discovery. It is noteworthy that for the first time, the derivation of iPSC lines from the whole blood of children with ASD was recently described (DeRoşa et al., 2012).

The lack of longitudinal studies in autism remains a striking gap in studies of brain function. While cross-sectional studies have provided important findings, there is a dearth of essential information about the time course of brain development from early infancy to adulthood (as well as the yet to be studied aging brain) in ASD. The power of longitudinal studies was recently reinforced by the results of a longitudinal structural MRI study that identified an increased rate of amygdala growth in very young children with ASD (Nordahl et al, 2012).

Although a network has been launched to study ASD in females, there remains a pressing need to conduct research aimed at understanding all aspects of ASD (genes, brain, and behavior) in females with ASD. ASD disproportionately affect males, and this skewed sex ratio has resulted in a bias of published research towards studies focused on males. Interestingly, girls are much less likely to be diagnosed with autism than are boys unless they also have intellectual or behavioral problems (Dworzynski et al., 2012), which might reflect either a gender bias in diagnosis or genuinely better adaptation/compensation in girls.

As more insight into the biological mechanisms underlying ASD is gained, one area that has been identified as a new gap is the role of the immune system and microglia in autism, which have recently been found to contribute to brain development and plasticity (Stephan, Barres & Stevens, 2012). Another is to understand the generalizability and pathophysiological significance of the findings of increased oxidative stress markers in plasma of children with autism (Melnyk et al., 2011). Further investigation into these and other gap areas will help explain the underlying biology of ASD, aiding in the identification of biomarkers for diagnosis and informing potential treatments and interventions in the future.

References:

Abdallah MW, Larsen N, Mortensen EL, Atladóttir HÓ, Nørgaard-Pedersen B, Bonefeld-Jørgensen EC, Grove J, Hougaard DM. Neonatal levels of cytokines and risk of autism spectrum disorders: An exploratory register-based historic birth cohort study utilizing the Danish Newborn Screening Biobank. *J Neuroimmunol*. 2012 Nov 15;252(1-2):75-82. [PMID: 22917523]

Auerbach BD, Osterweil EK, Bear MF. Mutations causing syndromic autism define an axis of synaptic pathophysiology. *Nature*. 2011 Nov 23;480(7375):63-8. [PMID: 22113615]

Braunschweig D, Golub MS, Koenig CM, Qi L, Pessah IN, Van de Water J, Berman RF. Maternal autism-associated IgG antibodies delay development and produce anxiety in a mouse gestational transfer model. *J Neuroimmunol*. 2012 Nov 15;252(1-2):56-65. [PMID: 22951357]

Buckley AW, Rodriguez AJ, Jennison K, Buckley J, Thurm A, Sato S, Swedo S. Rapid eye movement sleep percentage in children with autism compared with children with developmental delay and typical development. Arch Pediatr Adolesc Med. 2010 Nov;164(11):1032-7. [PMID: 21041596]

Davidovitch M, Golan D, Vardi O, Lev D, Lerman-Sagie T. Israeli children with autism spectrum disorder are not macrocephalic. *J Child Neurol*. 2011 May;26(5):580-5. [PMID: 21464237]

DeRosa BA, Van Baaren JM, Dubey GK, Lee JM, Cuccaro ML, Vance JM, Pericak-Vance MA, Dykxhoorn DM. Derivation of autism spectrum disorder-specific induced pluripotent stem cells from peripheral blood mononuclear cells. *Neurosci Lett*. 2012 May 10;516(1):9-14. [PMID: 22405972]

Dworzynski K, Ronald A, Bolton P, Happé F. How different are girls and boys above and below the diagnostic threshold for autism spectrum disorders? *J Am Acad Child Adolesc Psychiatry*. 2012 Aug;51(8):788-97. [PMID: 22840550]

Elsabbagh M, Mercure E, Hudry K, Chandler S, Pasco G, Charman T, Pickles A, Baron-Cohen S, Bolton P, Johnson MH; BASIS Team. Infant neural sensitivity to dynamic eye gaze is associated with later emerging autism. *Curr Biol*. 2012 Feb 21;22(4):338-42. [PMID: 22285033]

ENCODE Project Consortium. An integrated encyclopedia of DNA elements in the human genome. *Nature*. 2012 Sep 6;489(7414):57-74. [[PMID: 22955616]]

ENCODE Project Consortium, Dunham I, Kundaje A, Aldred SF, Collins PJ, Davis CA, Doyle F, Epstein CB, Frietze S, Harrow J, Kaul R, Khatun J, Lajoie BR, Landt SG, Lee BK, Pauli F, Rosenbloom KR, Sabo P, Safi A, Sanyal A, Shoresh N, Simon JM, Song L, Trinklein ND, Altshuler RC, Birney E, Brown JB, Cheng C, Djebali S, Dong X, Dunham I, Ernst J, Furey TS, Gerstein M, Giardine B, Greven M, Hardison RC, Harris RS, Herrero J, Hoffman MM, Iyer S, Kelllis M, Khatun J, Kheradpour P, Kundaje A, Lassman T, Li Q, Lin X, Marinov GK, Merkel A, Mortazavi A, Parker SC, Reddy TE, Rozowsky J, Schlesinger F, Thurman RE, Wang J, Ward LD, Whitfield TW, Wilder SP, Wu W, Xi HS, Yip KY, Zhuang J, Bernstein BE, Birney E, Dunham I, Green ED, Gunter C, Snyder M, Pazin MJ, Lowdon RF, Dillon LA, Adams LB, Kelly CJ, Zhang J, Wexler JR, Green ED, Good PJ, Feingold EA, Bernstein BE, Birney E, Crawford GE, Dekker J, Elinitski L, Farnham PJ, Gerstein M, Giddings MC, Gingeras TR, Green ED, Guigó R, Hardison RC, Hubbard TJ, Kellis M, Kent WJ, Lieb JD, Margulies EH, Myers RM, Snyder M, Starnatoyannopoulos JA, Tennebaum SA, Weng Z, White KP, Wold B, Khatun J, Yu Y, Wrobel J, Risk BA, Gunawardena HP, Kuiper HC, Maier CW, Xie L, Chen X, Giddings MC, Bernstein BE, Epstein CB, Shoresh N, Ernst J, Kheradpour P, Mikkelsen TS, Gillespie S, Goren A, Ram O, Zhang X, Wang L, Issner R, Coyne MJ, Durham T, Ku M,

Truong T, Ward LD, Altshuler RC, Eaton ML, Kellis M, Djebali S, Davis CA, Merkel A, Dobin A, Lassmann T, Mortazavi A, Tanzer A, Lagarde J, Lin W, Schlesinger F, Xue C, Marinov GK, Khatun J, Williams BA, Zaleski C, Rozowsky J, Röder M, Kokocinski F, Abdelhamid RF, Alioto T, Antoshechkin I, Baer MT, Batut P, Bell I, Bell K, Chakrabortty S, Chen X, Chrast J, Curado J, Derrien T, Drenkow J, Dumais E, Dumais J, Duttagupta R, Fastuca M, Fejes-Toth K, Ferreira P, Foissac S, Fullwood MJ, Gao H, Gonzalez D, Gordon A, Gunawardena HP, Howald C, Jha S, Johnson R, Kapranov P, King B, Kingswood C, Li G, Luo OJ, Park E, Preall JB, Presaud K, Ribeca P, Risk BA, Robyr D, Ruan X, Sammeth M, Sandu KS, Schaeffer L, See LH, Shahab A, Skancke J, Suzuki AM, Takahashi H, Tilgner H, Trout D, Walters N, Wang H, Wrobel J, Yu Y, Hayashizaki Y, Harrow J, Gerstein M, Hubbard TJ, Reymond A, Antonarakis SE, Hannon GJ, Giddings MC, Ruan Y, Wold B, Carninci P, Guigó R, Gingeras TR, Rosenbloom KR, Sloan CA, Learned K, Malladi VS, Wong MC, Barber GP, Cline MS, Dreszer TR, Heitner SG, Karolchik D, Kent WJ, Kirkup VM, Meyer LR, Long JC, Maddren M, Raney BJ, Furey TS, Song L, Grasfeder LL, Giresi PG, Lee BK, Battenhouse A, Sheffield NC, Simon JM, Showers KA, Safi A, London D, Bhinge AA, Shestak C, Schaner MR, Kim SK, Zhang ZZ, Mieczkowski PA, Mieczkowska JO, Liu Z, McDaniell RM, Ni Y, Rashid NU, Kim MJ, Adar S, Zhang Z, Wang T, Winter D, Keefe D, Birney E, Iyer VR, Lieb JD, Crawford GE, Li G, Sandhu KS, Zheng M, Wang P, Luo OJ, Shahab A, Fullwood MJ, Ruan X, Ruan Y, Myers RM, Pauli F, Williams BA, Gertz J, Marinov GK, Reddy TE, Vielmetter J, Partridge EC, Trout D, Varley KE, Gasper C, Bansal A, Pepke S, Jain P, Amrhein H, Bowling KM, Anaya M, Cross MK, King B, Muratet MA, Antoshechkin I, Newberry KM, McCue K, Nesmith AS, Fisher-Aylor KI, Pusey B, DeSalvo G, Parker SL, Balasubramanian S, Davis NS, Meadows SK, Eggleston T, Gunter C, Newberry JS, Levy SE, Absher DM, Mortazavi A, Wong WH, Wold B, Blow MJ, Visel A, Pennachio LA, Elnitski L, Margulies EH, Parker SC, Petrykowska HM, Abyzov A, Aken B, Barrell D, Barson G, Berry A, Bignell A, Boychenko V, Bussotti G, Chrast J, Davidson C, Derrien T, Despacio-Reyes G, Diekhans M, Ezkurdia I, Frankish A, Gilbert J, Gonzalez JM, Griffiths E, Harte R, Hendrix DA, Howald C, Hunt T, Jungreis I, Kay M, Khurana E, Kokocinski F, Leng J, Lin MF, Loveland J, Lu Z, Manthravadi D, Mariotti M, Mudge J, Mukherjee G, Notredame C, Pei B, Rodriguez JM, Saunders G, Sboner A, Searle S, Sisu C, Snow C, Steward C, Tanzer A, Tapanan E, Tress ML, van Baren MJ, Walters N, Washieti S, Wilming L, Zadissa A, Zhengdong Z, Brent M, Haussler D, Kellis M, Valencia A, Gerstein M, Raymond A, Guigó R, Harrow J, Hubbard TJ, Landt SG, Frietze S, Abyzov A, Addleman N, Alexander RP, Auerbach RK, Balasubramanian S, Bettinger K, Bhardwaj N, Boyle AP, Cao AR, Cayting P, Charos A, Cheng Y, Cheng C, Eastman C, Euskirchen G, Fleming JD, Grubert F, Habegger L, Hariharan M, Harmanci A, Iyenger S, Jin VX, Karczewski KJ, Kasowski M, Lacroute P, Lam H, Larnarre-Vincent N, Leng J, Lian J, Lindahl-Allen M, Min R, Miotto B, Monahan H, Moqtaderi Z, Mu XJ, O'Geen H, Ouyang Z, Patacsil D, Pei B, Raha D, Ramirez L, Reed B, Rozowsky J, Sboner A, Shi M, Sisu C, Slifer T, Witt H, Wu L, Xu X, Yan KK, Yang X, Yip KY, Zhang Z, Struhl K, Weissman SM, Gerstein M, Farnham PJ, Snyder M, Tenebaum SA, Penalva LO, Doyle F, Karmakar S, Landt SG, Bhanvadia RR, Choudhury A, Domanus M, Ma L, Moran J, Patacsil D, Slifer T, Victorsen A, Yang X, Snyder M, White KP, Auer T, Centarin L, Eichenlaub M, Gruhl F, Heerman S, Hoeckendorf B, Inoue D, Kellner T, Kirchmaier S, Mueller C, Reinhardt R, Schertel L, Schneider S, Sinn R, Wittbrodt B, Wittbrodt J, Weng Z, Whitfield TW, Wang J, Collins PJ, Aldred SF, Trinklein ND, Partridge EC, Myers RM, Dekker J, Jain G, Lajoie BR, Sanyal A, Balasundaram G, Bates DL, Byron R, Canfield TK, Diegel MJ, Dunn D, Ebersol AK, Ebersol AK, Frum T, Garg K, Gist E, Hansen RS, Boatman L, Haugen E, Humbert R, Jain G,

Johnson AK, Johnson EM, Kutyavin TM, Lajoie BR, Lee K, Lotakis D, Maurano MT, Neph SJ, Neri FV, Nguyen ED, Qu H, Reynolds AP, Roach V, Rynes E, Sabo P, Sanchez ME, Sandstrom RS, Sanyal A, Shafer AO, Stergachis AB, Thomas S, Thurman RE, Vernot B, Vierstra J, Vong S, Wang H, Weaver MA, Yan Y, Zhang M, Akey JA, Bender M, Dorschner MO, Groudine M, MacCoss MJ, Navas P, Stamatoyannopoulos G, Kaul R, Dekker J, Stamatoyannopoulos JA, Dunham I, Beal K, Brazma A, Flicek P, Herrero J, Johnson N, Keefe D, Lukk M, Luscombe NM, Sobral D, Vaquerizas JM, Wilder SP, Batzoglou S, Sidow A, Hussami N, Kyriazopoulou-Panagiotopoulou S, Libbrecht MW, Schaub MA, Kundaje A, Hardison RC, Miller W, Giardine B, Harris RS, Wu W, Bickel PJ, Banfai B, Boley NP, Brown JB, Huang H, Li Q, Li JJ, Noble WS, Bilmes JA, Buske OJ, Hoffman MM, Sahu AO, Kharchenko PV, Park PJ, Baker D, Taylor J, Weng Z, Iyer S, Dong X, Greven M, Lin X, Wang J, Xi HS, Zhuang J, Gerstein M, Alexander RP, Balasubramanian S, Cheng C, Harmanci A, Lochovsky L, Min R, Mu XJ, Rozowsky J, Yan KK, Yip KY, Birney E. An integrated encyclopedia of DNA elements in the human genome. *Nature*. 2012 Sep 6;489(7414):57-74. [PMID: 22955616]

Greene DJ, Colich N, Iacoboni M, Zaidel E, Bookheimer SY, Dapretto M. Atypical neural networks for social orienting in autism spectrum disorders. *Neuroimage*. 2011 May 1;56(1):354-62. [PMID: 21334443]

Gotts SJ, Simmons WK, Milbury LA, Wallace GL, Cox RW, Martin A. Fractionation of social brain circuits in autism spectrum disorders. *Brain*. 2012 Sep;135(Pt 9):2711-25. [PMID: 22791801]

Guiraud JA, Tomalski P, Kushnerenko E, Ribeiro H, Davies K, Charman T, Elsabbagh M, Johnson MH; BASIS Team. Atypical audiovisual speech integration in infants at risk for autism. *PLoS One*. 2012;7(5):e36428. 2012 May 15. [Epub ahead of print] [PMID: 22615768]

Hoeft F, Walter E, Lightbody AA, Hazlett HC, Chang C, Piven J, Reiss AL. Neuroanatomical differences in toddler boys with fragile x syndrome and idiopathic autism. *Arch Gen Psychiatry*. 2011 Mar;68(3):295-305. [PMID: 21041609]

Hsiao EY, McBride SW, Chow J, Mazmanian SK, Patterson PH. Modeling an autism risk factor in mice leads to permanent immune dysregulation. *Proc Natl Acad Sci USA*. 2012 Jul 31;109(31):12776-81. doi: 10.1073/pnas.1202556109. 2012 Jul 16. [Epub ahead of print] [PMID: 22802640]

Hsiao EY, Patterson PH. Placental regulation of maternal-fetal interactions and brain development. *Dev Neurobiol*. 2012 Oct;72(10):1317-26. doi: 10.1002/dneu.22045. 2012 Aug 23. [Epub ahead of print]

[PMID: 22753006]

Human Microbiome Project Consortium. Structure, function, and diversity of the healthy human microbiome. *Nature.* 2012 Jun 13;486(7402):207-14. [PMID: 22699609].

Kliemann D, Dziobek I, Hatri A, Baudewig J, Heekeren HR. The role of the amygdala in atypical gaze on emotional faces in autism spectrum disorders. *J Neurosci*. 2012 Jul 11;32(28):9469-76. [PMID: 22787032]

Leblond CS, Heinrich J, Delorme R, Proepper C, Betancur C, Huguet G, Konyukh M, Chaste P, Ey E, Rastam M, Anckarsäter H, Nygren G, Gillberg IC, Melke J, Toro R, Regnault B, Fauchereau F, Mercati O, Lemière N, Skuse D, Poot M, Holt R, Monaco AP, Järvelä I, Kantojärvi K, Vanhala R, Curran S, Collier DA, Bolton P, Chiocchetti A, Klauck SM, Poustka F, Freitag CM, Waltes R, Kopp M, Duketis E, Bacchelli E, Minopoli F, Ruta L, Battaglia A, Mazzone L, Maestrini E, Sequeira AF, Oliveira B, Vicente A, Oliveira G, Pinto D, Scherer SW, Zelenika D, Delepine M, Lathrop M, Bonneau D, Guinchat V, Devillard F, Assouline B, Mouren MC, Leboyer M, Gillberg C, Boeckers TM, Bourgeron T. Genetic and functional analyses of SHANK2 mutations suggest a multiple hit model of autism spectrum disorders. *PLoS Genet*. 2012 Feb;8(2):e1002521. [PMID: 22346768]

Lewis WW, Sahin M, Scherrer B, Peters JM, Suarez RO, Vogel-Farley VK, Jeste SS, Gregas MC, Prabhu SP, Nelson CA 3rd, Warfield SK. Impaired Language Pathways in Tuberous Sclerosis Complex Patients with Autism Spectrum Disorders. *Cereb Cortex*. 2012 Jun 1. [Epub ahead of print] [PMID: 22661408]

Marini C, Darra F, Specchio N, Mei D, Terracciano A, Parmeggiani L, Ferrari A, Sicca F, Mastrangelo M, Spaccini L, Canopoli ML, Cesaroni E, Zamponi N, Caffi L, Ricciardelli P, Grosso S, Pisano T, Canevini MP, Granata T, Accorsi P, Battaglia D, Cusmai R, Vigevano F, Bernardina BD, Guerrini R. Focal seizures with affective symptoms are a major feature of PCDH19 gene-related epilepsy. *Epilepsia*. 2012 Sep 4. [Epub ahead of print] [PMID: 22946748]

Mazurek MO, Vasa RA, Kalb LG, Kanne SM, Rosenberg D, Keefer A, Murray DS, Freedman B, Lowery LA. Anxiety, Sensory Over-Responsivity, and Gastrointestinal Problems in Children with Autism Spectrum Disorders. *J Abnorm Child Psychol*. 2012 Aug 1. [Epub ahead of print] [PMID: 22850932]

Melnyk S, Fuchs GJ, Schulz E, Lopez M, Kahler SG, Fussell JJ, Belando J, Pavliv O, Rose S, Seidel S, Gaylor DW, James SJ. Metabolic imbalance associated with methylation dysregulation and oxidative damage in children with autism. *J Autism Developmental Disorder*. 2012 Mar; 42 (3) 367-377. [PMID: 21519954]

Nordahl CW, Lange N, Li DD, Barnett LA, Lee A, Buonocore MH, Simon TJ, Rogers S, Ozonoff S, Amaral DG. Brain enlargement is associated with regression in preschool-age boys with autism spectrum disorders. *Proc Natl Acad Sci USA*. 2011 Dec 13;108(50):20195-200. [PMID: 22123952]

Novarino G, El-Fishawy P, Kayserili H, Meguid NA, Scott EM, Schroth J, Silhavy JL, Kara M, Khalil RO, Ben-Omran T, Ercan-Sencicek AG, Hashish AF, Sanders SJ, Gupta AR, Hashem HS,

Matern D, Gabriel S, Sweetman L, Rahimi Y, Harris RA, State MW, Gleeson JG. Mutations in BCKD-kinase lead to a potentially treatable form of autism with epilepsy. *Science*. 2012 Oct 19;338(6105):394-7. [PMID: 22956686]

Paşca SP, Portmann T, Voineagu I, Yazawa M, Shcheglovitov A, Paşca AM, Cord B, Palmer TD, Chikahisa S, Nishino S, Bernstein JA, Hallmayer J, Geschwind DH, Dolmetsch RE. Using iPSC-derived neurons to uncover cellular phenotypes associated with Timothy syndrome. *Nat Med*. 2011 Nov 27;17(12):1657-62. [PMID: 22120178]

Redcay E, Dodell-Feder D, Mavros PL, Kleiner M, Pearrow MJ, Triantafyllou C, Gabrieli JD, Saxe R. Atypical brain activation patterns during a face-to-face joint attention game in adults with autism spectrum disorder. *Hum Brain Mapp*. 2012 Apr 16. [Epub ahead of print] [PMID: 22505330]

Rudie JD, Hernandez LM, Brown JA, Beck-Pancer D, Colich NL, Gorrindo P, Thompson PM, Geschwind DH, Bookheimer SY, Levitt P, Dapretto M. Autism-associated promoter variant in MET impacts functional and structural brain networks. *Neuron*. 2012 Sep 6;75(5):904-15. [PMID: 22958829]

Schafer DP, Lehrman EK, Kautzman AG, Koyama R, Mardinly AR, Yamasaki R, Ransohoff RM, Greenberg ME, Barres BA, Stevens B. Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner. *Neuron*. 2012 May 24;74(4):691-705. [PMID: 22632727]

Schmeisser MJ, Ey E, Wegener S, Bockmann J, Stempel AV, Kuebler A, Janssen AL, Udvardi PT, Shiban E, Spilker C, Balschun D, Skryabin BV, Dieck St, Smalla KH, Montag D, Leblond CS, Faure P, Torquet N, Le Sourd AM, Toro R, Grabrucker AM, Shoichet SA, Schmitz D, Kreutz MR, Bourgeron T, Gundelfinger ED, Boeckers TM. Autistic-like behaviours and hyperactivity in mice lacking ProSAP1/Shank2. Nature. 2012 Apr 29;486(7402):256-60. [PMID: 22699619]

Silverman JL, Smith DG, Rizzo SJ, Karras MN, Turner SM, Tolu SS, Bryce DK, Smith DL, Fonseca K, Ring RH, Crawley JN. Negative allosteric modulation of the mGluR5 receptor reduces repetitive behaviors and rescues social deficits in mouse models of autism. *Sci Transl Med*. 2012 Apr 25;4(131):131ra51. [PMID: 22539775]

Stephan AH, Barres BA, Stevens B. The complement system: an unexpected role in synaptic pruning during development and disease. *Annu Rev Neurosci*. 2012;35:369-89. [PMID: 22715882]

Taylor MA, Schreck KA, Mulick JA. Sleep disruption as a correlate to cognitive and adaptive behavior problems in autism spectrum disorders. Res Dev Disabil. 2012 Sep-Oct;33(5):1408-17. [PMID: 22522199]

Tordjman S, Anderson GM, Bellissant E, Botbol M, Charbuy H, Camus F, Graignic R, Kermarrec S, Fougerou C, Cohen D, Touitou Y. Day and nighttime excretion of 6-sulphatoxymelatonin in adolescents and young adults with autistic disorder. *Psychoneuroendocrinology*. 2012 Dec;37(12):1990-7. [PMID: 22613035]

Tsai PT, Hull C, Chu Y, Greene-Colozzi E, Sadowski AR, Leech JM, Steinberg J, Crawley JN, Regehr WG, Sahin M. Autistic-like behaviour and cerebellar dysfunction in Purkinje cell Tsc1 mutant mice. *Nature*. 2012 Aug 30;488(7413):647-51. [PMID: 22763451]

Voineagu I, Wang X, Johnston P, Lowe JK, Tian Y, Horvath S, Mill J, Cantor RM, Blencowe BJ, Geschwind DH. Transcriptomic analysis of autistic brain reveals convergent molecular pathology. *Nature*. 2011 May 25;474(7351):380-4. [PMID: 21614001]

Wedeen VJ, Rosene DL, Wang R, Dai G, Mortazavi F, Hagmann P, Kaas JH, Tseng WY. The geometric structure of the brain fiber pathways. *Science*. 2012 Mar 30;335(6076):1628-34. [PMID: 22461612]

Weinstein M, Ben-Sira L, Levy Y, Zachor DA, Ben Itzhak E, Artzi M, Tarrasch R, Eksteine PM, Hendler T, Ben Bashat D. Abnormal white matter integrity in young children with autism. *Hum Brain Mapp*. 2011 Apr;32(4):534-43. [PMID: 21391246]

Wolff JJ, Gu H, Gerig G, Elison JT, Styner M, Gouttard S, Botteron KN, Dager SR, Dawson G, Estes AM, Evans AC, Hazlett HC, Kostopoulos P, McKinstry RC, Paterson SJ, Schultz RT, Zwaigenbaum L, Piven J; IBIS Network. Differences in white matter fiber tract development present from 6 to 24 months in infants with autism. *Am J Psychiatry*. 2012 Jun;169(6):589-600. [PMID: 22362397]