Review

Autism Disease: Neural Network Going Awry and Therapeutic Strategy Underlying Neural Plasticity

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ABSTRACT

Autism is the major form of Autism Spectrum Disorders (ASD). Autism was first discovered in 1940s and has attracted enormous research and social activities recently. It is a disease currently defined only by behavior problems including impairments in communication, inability in social interactions, and stereotyped patterns of interest and behavior. Because of the complexity nature of the disease, there are many basic questions yet to be answered by scientific research. Autism is of great and increasing public health concern because the number of children receiving services is growing each year. In this commentary review, we will analyze recent studies on brain structure, genetics, and brain conditions and graph an overview of autism from these findings. Under the basis of synaptic plasticity, we believe the findings have led us to propose a hypothesis on therapeutic strategy, by which we may be able reshape the troubled neural network towards its normal networking function.

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KEY WORDS: *Autism Spectrum* Disorders, DSM-V, Rett's Syndrome

INTRODUCTION OF AUTISM AND AUTISM SPECTRUM DISORDERS

Autism disorder is discovered and described with the same disease name independently by two physicians, the American psychiatrist Leo Kanner and Austrian pediatrician Hans Asperger.[1,2] The terminology is derived from the Greek word 'autos' meaning 'self'. Intriguingly, the patients often reverse the normal use of pronouns, particularly using 'you' instead of 'I' or 'me' when referring to themselves.[1] In 1943, Leo Kanner published the classic paper Autistic Disturbances of Affective Contact. In the paper, he described a group of patients with excellent rote memories (such as remembering rhymes, lists, and numbers) but poor social and communication skills starting from infancy. In 1944, Hans Asperger published his original paper described a similar condition with similar social and communication difficulties similar to Kanner's autism but with relatively normal intelligence, now known as Asperger syndrome.[2] It was noticed that Asperger first created this terminology in his speech before both publications.[1] Largely based upon Kanner and Asperger's independent findings, we now define autism as a group of disease with shared characteristics including impaired social interactions, troubled inter-personal communications, restricted interests, and repetitive behaviors.[i] Most patients develop symptoms before the age of one year old, which might have been already emerging even at the time of birth, and all have onsets before age of 3.

One of the major reasons for autism attracting public interest and medical attention is that this is a highly popular disease, highlighted by a world-wide prevalence of approximately 0.2 percent. The other four subtypes of ASDs are either similarly common or less common than autism, including Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS or Atypical Autism) (0.15 percent prevalence), Rett's Syndrome (caused by MECP2 mutations or less commonly CDKL5 or FOXG1 mutations) (0.006 percent prevalence), Asperger's Disorder (ASP; a similar condition that is not associated with language delay or general intellectual impairments) (0.025 percent prevalence) and Childhood Disintegrative Disorder (CDD; usually a normal development followed by an abrupt recession of brain functions) (0.001 percent prevalence).[7] The estimated prevalence of ASD in the US is 1 in 110.[8] It is noteworthy that in 2000 US Centers for Disease Control and Prevention (CDC) have built a group of programs named the Autism and Developmental Disabilities Monitoring (ADDM) Network to track the prevalence and characteristics of ASDs in the country.[9] The prevalence of autism in the US has kept increasing each year after the initial discovery of the disorder.

Autism spectrum disorders and autism are now classified under the category of Neuordevelopmental Disorders in the revising fifth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-V) (in development, expected publication after July 15, 2011) by the American Psychiatric Association.[10] In DSM-IV it has been classified under the category of Pervasive Developmental Disorders (PDD). According to DSM-V, a person must have all four characteristics below for the diagnosis of ASD; therefore, diagnosis of autism must also meet all of the parameters of

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the following four aspects in DSM-V (with minor corrections for typo and punctuation for consistency by the author):

A. Persistent deficits in social communication and social interaction across contexts, not accounted for by general developmental delays, and manifest by all 3 of the following:

1. Deficits in social-emotional reciprocity; ranging from abnormal social approach and failure of normal back and forth conversation through reduced sharing of interests, emotions, and affect and response, to total lack of initiation of social interaction.

2. Deficits in nonverbal communicative behaviors used for social interaction; ranging from poorly integrated- verbal and nonverbal communication, through abnormalities in eye contact and body-language, or deficits in understanding and use of nonverbal communication, to total lack of facial expression or gestures.

3. Deficits in developing and maintaining relationships appropriate to developmental level (beyond those with caregivers); ranging from difficulties adjusting behavior to suit different social contexts through difficulties in sharing imaginative play and in making friends, to an apparent absence of interest in people.

B. Restricted, repetitive patterns of behavior, interests, or activities as manifested by at least 2 of the following:

1. Stereotyped or repetitive speech, motor movements, or use of objects; (such as simple motor stereotypes, echolalia, repetitive use of objects, or idiosyncratic phrases).

2. Excessive adherence to routines, ritualized patterns of verbal or nonverbal behavior, or excessive resistance to change; (such as motoric rituals, insistence on same route or food, repetitive questioning or extreme distress at small changes).

3. Highly restricted, fixated interests that are abnormal in intensity or focus; (such as strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests).

4. Hyper-or hypo-reactivity to sensory input or unusual interest in sensory aspects of environment; (such as apparent indifference to pain/heat/cold, adverse response to specific sounds or textures, excessive smelling or touching of objects, fascination with lights or spinning objects).

C. Symptoms must be present in early childhood (but may not become fully manifest until social demands exceed limited capacities).

D. Symptoms together limit and impair everyday functioning.

Currently autism is largely regarded and cared as a social problem for physically normal patients. Many of them have received public support such as from professional and public societies as well as commercial trainings. A significant proportion of patients have complications including epilepsy and anxiety that are associated with the disease. These patients are frequently under drug treatment to control symptoms. A collection of drugs for officially (FDA) recognized indications to autism, as well as off-label treatment (a much larger proportion), are listed below.

In the rest part of the review, we will focus on autism (rather than ASD) for its abnormal brain features, genetic defect profiles, oxidative stress related physical conditions, and the concept of neural plasticity, and from these analyses, we hope to depict an overall picture towards the hypothesis for neuroplasticity based therapy for autism patients.

Table 1. Drug for treating symptoms and complications in autism patients. (From source that is updated in 2011[11])

Part 1: US Food and Drug Administration (FDA) approved drugs for autism:

Name	Generic Name	Description
Abilify	aripiprazole	This antidepressant was recently approved by the FDA in the United States for the treatment of irritability associated with autistic disorder in pediatric patients 6 to 17 years of age.
Risperdal	risperidone	This oral psychotropic medication is used to treat aggression, irritability, and severe behavior problems in autistic children 5-16 years old.

Part 2: Off label treatment for autism: Drugs below approved for psychological disorders may also have therapeutic effects on autism that, however, are off-labeled. Clinicians can administer these drugs to autism patients for releasing related symptoms and improving social behaviors.

Name	Generic Name	Description
Actos Actoplus Met	pioglitazone hydrocloride pioglitazone hydrocloride and metformin hydrochloride	Both Actos and Actoplus Met are being tested in people with neurological disorders, including autism, because it can also be anti-inflammatory in glial cells in the brain. Preliminary studies showed improvements in behavior in children with autism.
Adderall	amphetamine	Adderall is a central nervous system stimulant that affects chemicals in the brain and in nerves. These brain chemicals (neurotransmitters) regulate activity and impulse control. Adderall may be prescribed off-label for people with autism. Caution: amphetamines have a high potential for abuse and addiction.
Anafranil	clomipramine hydrocloride	Anafranil is an antidepressant that may be prescribed off-label for children with autism to help decrease repetitive movements and improve social contacts
Aricept	donepezil hydrochloride	Aricept enhances cholinergic function in the brain by reducing the activity of the enzyme acetyl cholinesterase. In people with autism, Aricept may help improve attention, learning, and memory. Possible benefits of Aricept are being tested in children and adults with autism, as well as ADHD and schizophrenia.
Ativan	lorazepam	Ativan is an anti-anxiety medication that may be prescribed for people with autism to help reduce anxiety, and to help reduce symptoms of catatonia(rigid and insensitive muscles). Ativan is indicated for treatment of anxiety disorders.
Bethanechol	bethanechol chloride	Bethanechol is prescribed for triggering urination and emptying of the bladder when urine is being retained in autism patients.
Buspar	buspirone hydrochloride	Buspar is an antianxiety medication that is indicated for generalized anxiety disorder. Buspar may be prescribed off-label for people with autism to help reduce anxiety and aggression and to help improve behaviors. Buspar has helped improve behaviors in some people with autism. This medication is currently being tested in children and adults with autism.
Carbatrol - Equetro -Tegretol	carbamazepine	Carbamazepine is the generic for three brand name drugs, Carbatrol, Equetro, and Tegretol. Tegretol is an anticonvulsant medication used to help control seizures. Tegretol may be prescribed for people with autism who have seizures, and can also help soften mood swings. Carbatrol may be prescribed for people with autism who have seizures, and can also help reduce aggression. Equetro is an extended-release formulation of carbamazepine. It is indicated for the treatment of mania in bipolar disorder. Equetro can have serious side effects that include agranulocytosis and other changes in blood cells, so the person taking this medication should be monitored with regular blood tests. Note: Carbamazepine can have serious side effects with a certain genetic background.
Clozaril -FazaClo	clozapine	This is an antipsychotic medication that may be prescribed off-label for children with autism to help reduce hyperactivity, fidgeting, and aggression. Clozaril® lowers binding of dopamine to most types of dopamine receptorsand other types of receptors on cells in the nervous system.

Concerta	methylphenidate hydrochloride	Some children with autism also have ADHD and this drug may be helpful in treating the symptoms of ADHD.
Depakene	valproic acid	Depakene affects the way that cells get signals to turn on and off in the nervous system. People with autism who also have seizures might be prescribed this medication.
Depakote	divalproex sodium	Depakote is an anticonvulsant used to treat epilepsy. People with autism who also have seizures might be prescribed this medication.
Dexedrine - Dexedrine Spansule	dextroamphetamine sulfate	Dexedrine may be prescribed off-label for hyperactivity in children with autism. Dextroamphetamine sulfate is an amphetamine that stimulates the brain and nervous system. Caution: Amphetamines have a high potential for abuse and may lead to drug dependence.
Diastat	diazepam	Diastat may be prescribed for people with autism who also have epilepsy, and would usually be administered as short term treatment during the seizure.
Diflucan	fluconazole	Diflucan is an anti-fungal antibiotic that is prescribed to treat fungus infections in any part of the body. Diflucan may be prescribed off-label for children with autism to help relieve their autism symptoms, based on the idea that autism symptoms may be related to fungus infections in children.
Dilantin	phenytoin sodium	Dilantin is an antiepileptic drug that is indicated for helping to control seizures in children and adults with autism.
Endrate	edetate disodium	Endrate is administered I.V., and recommended only for severe cases of metal poisoning and prescribed for emergency treatment of hypercalcemia as chelation therapy in children with autism.
Eskalith	lithium carbonate	Eskalith (lithium carbonate): Eskalith® is anantidepressant that may be prescribed off-label for children with autism. The safety andeffectiveness of Eskalith in children with autismhas not been proven but it may be helpful for some of them.
Fortamet - Glumetza	metformin hydrochloride	Metformin works by decreasing liver glucose production, and increasing sensitivity to insulin in muscle and fat tissue. In people with autism, taking metformin with antipsychotic medications such as risperidone may help reduce weight gain that often occurs as a side effect of the antipsychoticmedication.
Geodon	ziprasidone	Geodon is an antipsychotic medication that may be prescribed for people with autism to help reducehyperactivity, aggression, self-abusive behavior, temper tantrums, lability (mood swings), social withdrawal, and repetitive behaviors. Geodon is currently in clinical trials to test effectiveness in children with autism. Some children have improved with treatment. Geodon works as adopamine and serotonin type 2 antagonist, and has other effects on the nervous system.
Haldol	haloperidol	Haldol is an antipsychotic medication that may be prescribed for some people with autism to help control aggression.
Inderal	propranolol hydrochloride	Known as a beta-blocker, Inderal being studied as a treatmentfor severe aggression in children with autism.
Klonopin	clonazepam	Clonazepam is indicated for use to treat seizure disorders and panic disorder. It may also be prescribed off-label for other conditions.
Invega	paliperidone	Paliperidone is indicated for treatment ofschizophrenia in adults. It may be prescribed off-label for children with autism. Invega belongs to a class of drugs called atypical antipsychotics.
Lamictal	lamotrigine	Lamictal is an anticonvulsant and mood stabilizer that may be prescribed off-

		label for people withautism to help reduce lethargy (tiredness),irritability, hyperactivity. It may also improvelanguage, communication, and social skills.
Luvox	fluvoxamine maleate	Luvox is an antidepressant that may be prescribedoff-label for people with autism to help decreaserepetitive movements and improve social contacts.
Mycostatin	nystatin	Oral medication is Nystatin; cream form is Mycostatin. Mycostatin and Nystatin are prescribed to treat fungal infections of the skin, mouth, vagina, and intestinal (digestive) tract.
Namenda	memantine hydrochloride	Namenda may be prescribed off-label for people with autism in an effort to help improve language, social behavior, and other behaviors. Namenda is a glutamatereceptor antagonist (inhibits glutamate binding to its receptors).
Paxil	paroxetine	Paroxetine is an antidepressant that is a type ofselective serotonin reuptake inhibitor (SSRI). It works by restoring the balance of serotonin, aneurotransmitter in the brain, which helps to improve certain mood problems. Paxil® may also be prescribed for people with autism.
Pepcid	famotidine	Pepcid is a type of histamine-2 blockers that decreases the amount of acid that the stomach produces. Pepcid® is used to treat and prevent ulcers in the stomach and intestines. It also treats other conditions in which the acid produced by the stomach is a problem, such as gastroesophageal reflux disease (GERD) and heartburn.
Provigil	modafinil	Provigil promotes wakefulness. Off-label,modafinil is used by sleep deprived people to stay awake and to treat fatigue in autism.
Prozac	fluoxetine hydrochloride	Prozac is an antidepressant that may be prescribed for people with autism to help decreaseaggression and depression. It can also help reduce repetitive behaviors, and improve languageand social interactions.
Remeron	mirtazapine	Mirtazapine is an antidepressant that adjusts thebalance of neurotransmitters like norepinephrine and serotonin in the brain. Mirtazapinemay also be prescribed off-label for children withautism.
Revia -Vivitrol	naltrexone	This medication may be prescribed for autistic children to help improve ability to socialize and make eye contact, and also to help reduce painsensitivity, self-injury behaviors, and repetitive behaviors. This drug is an opioid antagonist, so it binds to opioid receptors and blocks the binding of alcohol or other drugs to thereceptors, thus blocking the opiates from having an effect so the person will stop their addiction. Some children with autism have higher than normal levels of beta-endorphins in their nervous system, and naltrexone can lower beta-endorphin levels.
Ritalin -Methylin	methylphenidate hydrochloride	Ritalin and Methylin are mild central nervous system stimulants that may be prescribed for people with autism to help reduce hyperactivity and repetitive movements.
Rozerem	ramelteon	Ramelteon is an oral medication (tablets) fortreatment of insomnia (an inability to sleep well).Ramelteon stimulates melatonin receptors in thenervous system, thereby promoting sleepiness. Many children with autism have problems sleepingand ramelteon is currently being tested foreffectiveness in children with autism.
Sarafem	fluoxetine hydrochloride	Sarafem is an antidepressant that may be prescribed for people with autism to help decreaseaggression and depression. It can also help reduce repetitive behaviors, and improve languageand social interactions.
Sporanox	itraconazole	Sporanox is prescribed to treat serious fungal infections which may invade any part of the body including mouth, throat, lungs, or nails.

Stablon -Coaxil - Tatinol	tianeptine	Tianeptine is a serotonin reuptake enhancer. This mechanism of action differs from manyantidepressants that are serotonin reuptake inhibitors.
Strattera	atomoxetine hydrochloride	Strattera may be prescribed off-label for people with autism to help with hyperactivity, obsessions, and other behavior problems. Stratteraworks by changing the ways some neurons are turned on and off.
Symbyax	fluoxetine hydrochloride and olanzapine	Symbyax contains an antidepressant (fluoxetine) and an antipsychotic (olanzapine). Symbyax may be prescribed for people with autism to decreaseanger, aggression, and repetitive movements; and to improve social interactions.
Tenex -Intuniv	guanfacine	Tenex or Intuniv (extended release form) stimulates certain receptors in the brain and nervous system. Guanfacine is indicated for lowering blood pressure and may also be prescribed off-label for sleep disorders, post-traumatic stress disorder, anti-social behaviors, oppositional disorder, and Tourette's disorder.
Thorazine - Thorazine Spansule	chlorpromazine	Thorazine may be prescribed for the treatment of severe behavioral problems such as combativeness and/or explosive hyperexcitable behavior.
Tofranil	imipramine hydrochloride	Tofranil is a tricyclic antidepressant that is usually prescribed for depression, and for childhood enuresis (bed-wetting).
Topamax	topiramate	Topamax is an anticonvulsant that may be prescribed for people with autism to help reduceirritability and self-injuring behaviors.
Trileptal	oxcarbazepine	This anti-seizure medication affects the way neurons are turned on and off. People with autism who also have seizures might be prescribed this medication.
Valium -Diastat	diazepam	Valium is a sedative that may be prescribed for people with autism to help reduce aggression and anxiety, or for seizures.
Versenate	edetate calcium disodium	Versenate chelates or strongly binds to divalent and trivalent metals including lead, zinc, cadmium, manganese, iron, and mercury. Versenate may be used in children with autism to reduce heavy metals in their body in an effort to improve behaviors.
Xanax	alprazolam	Alprazolam helps restore chemical balance in the brain when there are imbalances that may cause anxiety. It may also be prescribed off-label for people withautism. Caution: alprazolam may be habit-forming.
Zoloft	sertraline hydrochloride	Zoloft is an antidepressant that may be prescribed to help reduce anxiety and repetitive behaviors in people with autism. This medication is aserotonin reuptake inhibitor (SSRI).
Zyprexa	olanzapine	Zyprexa is a psychotropic medication that may be prescribed off-label for people with autism to reduce disruptive and repetitive behaviors. Zyprexa works as a dopamineand serotonin type 2 antagonist, and has other effects on the nervous system.

NEUROIMAGING ABNORMALITY OF AUTISM IS CHARACTERIZED BY PAN-BRAIN INVOLVEMENT

Three types of techniques have been utilized to identify brain abnormalities in autism. These include head circumference measurement, postmortem anatomy, and neuroimaging. Neuroimaging has been the most promising technique to unravel the structural and functional changes of autism brain. To explore the significance of neurobiology findings on autism, it would be necessary to summarize the application of i*n vivo* imaging technology and the progress in human brain mapping.

Mapping human brain has been mainly benefited from advanced neuroimaging technologies. Positron emission tomography (PET), magnetic resonance imaging (MRI), functional MRI (fMRI) and neurospectroscopy have been applied to autism research.[12] PET detects gamma rays from pulsed radioactive material (a blood sugar analog) to track brain blood flow. Based upon the high fidelity correlation

between brain activity and blood supply, PET produces three-dimensional images and records changes of brain blood flow. Modern PET scanners acquire the images with the aid of computerized tomography scan (CT scan), namely PET/CT scan. PET based technology is a specific and sensitive method for brain function analysis. This technology has serious limitations due to the use of on-site generated radio-tracers.[13] MRI, which wins the Nobel Prize in 1980, revolutionarily contributed to medical and neural imaging field. MRI utilized magnitude field to realign the brain water protons and detect the diffusion of water molecule during magnitude releasing. A several minute scan can provide more than 100 pictures of tissue slices visualizing the entire brain. Detail and accurate structures of only 1mm in size can be identified for the most part of brain.[14] MRI technology is non-invasive, non-radioactive, and has been proved safe from more than 30 years of use. MRI is the most powerful in vivo technique to characterize live brain structures. The further developed MRI, fMRI, combines MRI with blood flow detection technique to accurately examine activated brain area. fMRI is the major technology to localize and map the functionality of the brain. Neurospectroscopy (MR-spectroscopy, or MRS) is a newly developed imaging technology which records protons from various tissue chemicals other than water (unlike MRI), such as intrinsic phosphorus containing metabolites, sodium, potassium, carbon, nitrogen, and fluorine. MRS provides the possibility to record human and animal brain biochemistry in vivo. The combination of MRS with PET or MRI may create a powerful platform for mapping human brain in normal and pathophysiological conditions such as autism.[15]

Neuroimaging-based studies on brain mapping highlight the integrity and interactions between cortex and limbic system, between left and right hemispheres, and between the already-built structure and the neural plasticity of human brain. A functionally efficient human brain is depend upon the well developed cerebral cortex and sub-cortical structures, coordination between both hemispheres, and modifiability of developed, matured brain. Functional brain mapping suggests that human brain is constantly under dynamic reconstruction adjusting from the change of environment. Although infants already have approximately 100 billion neurons at birth that is the similar amount to adults, the neurons are largely separated from each other and not well myelinated.[16] They are relatively inactive in communication and work separately as single cellular units. In the early period of life, the most important activity is the maturation process by establishing neuronal networking across the brain. The first two years of life is the most critical stage for establishing the network towards a highly functional system.[6] The maturation process is largely dependent upon the genetic programming that is adapted to personal development of human being. Recent study of human brain has suggested that this system is altered in genetic psychological disorders including autism.[17,18]

The first finding on autism brain abnormality is probably the enlarged brain size. This finding has provided important clue to autism's underlying pathology. Kanner first noticed autism patients had relatively large head size in his clinics (Kanner 1943).[1] Other early reports also suggested that children with autism had enlarged brain size.[19] Clinical analysis has confirmed this disease feature in broad population. Systematic clinical examination, post-mortem and MRI studies have revealed that increased head circumference (macrocephaly), brain weight.[20,21] and brain volume.[22,23,24] were a gross anatomic feature of autism. The finding of brain enlargement in autism appears to be widely noticed. These abnormalities could be resulted from several problematic developmental processes that cause increased neurogenesis, enhanced myelination and decreased neuronal elimination.[25]

Researchers have examined available data from literature on the entire developmental course of brain enlargement in autism. They found that the enlargement is time-delimited to the first 2-4 years of life. There are three stages of the size change during autism childhood life - a reduced or normal brain size at birth, an early rapid rate of brain growth before year 2, and an abrupt cessation of growth by years 2-4.[26] Acceleration of brain growth in early age followed by a dramatic deceleration is a consistent finding in autism. This early cessation of growth results in a 2-4 year old autistic brain size that is similar to a normal adolescent or adult in majority of cases. At the age of 3-4, the period of pathological growth and arrest has likely already passed. Since autism pathology might develop mainly in the first years of life which is typically prior to the clinical diagnosis, by the time of diagnosis, clinicians and researchers often face a structure-wise "permanent" outcome.[27]

Further studies by neuroimaging seemed to have achieved very limited focuses on autism brain pathology. Despite growing number of quantitative MRI studies, only few robust findings have been observed. Some consistent findings from the main stream of research suggest the existence of morphometric abnormalities in several substructures in autism brain. Besides the total brain volume change, the structural abnormalities also involve the cerebellum, hippocampus, amygdala, corpus callosum, parieto-temporal lobe, and limbic- forebrain structures. The results have been noticed from well-designed MRI reports with satisfactory methodology. Among them, the size of corpus callosum may be reduced and amygdale may be increased.[25] While some of the structural changes are not yet of indicative about clinical manifestations, these two structures are highly interesting regarding the autism clinical characteristics. Amygdala is involved in emotional processing and therefore important in social interaction and cognitive functioning including of facial expression recognition, ability to gaze and interpretation of gaze, motion mimicking, visual alertness of potential threatening and hostile approaches.[5] There has been developed a proposal of an "amygdale theory of autism".[29] Lack of the related function might contribute to the social behavior and social intelligence deficits. Corpus callosum size reduction may diminish inter-hemispheric connectivity between relevant functional nuclei. The combination of both deficits may be involved in pathophysiology of the cognitive impairments of autism. It is still in debate about whether

frontal lobes are anatomically abnormal in autism, however considerable evidences from several controlled functional reports support that the pathophysiology likely exist due to cognitive impairment of autism.[30,31,32]

In summary, it is difficult to pinpoint the structural abnormalities but apparently easy to notice the overall change of autism brain - the abnormalities are rather generalized instead of localized, involving regions covering from the cortex, limbic system, to cerebellum, strongly suggest a troublesome brain system as a whole organ. It is now commonly accepted that autism has disturbed neural network involving cortical and subcortical areas, including temporo-parietal cortex, limbic system, cerebella, and prefrontal regions.

It is noteworthy that some well controlled MRI studies have showed negative findings in the size of certain brain structures including cerebellar vermis, brainstem, basal ganglia, and 4th ventricle, suggesting that these structures may be anatomically preserved but still deserve further investigation with advanced imaging technologies.[25] The quality of MRI-based neuroimaging investigations has steadily improved over recent years; still, many MRI studies seemed to be suffered from considerable methodological limitations, restricting the generalization of their findings. Longitudinal studies employing MRI would be preferential to tracking formation of abnormality of brain development to understand the neurobiology of autism. Future high quality quantitative MRI studies will need to be further carried out, with a focus on identifying possible morphological brain markers to further clarify the neural networks sustaining the pathophysiology of autism. Novel neuroimaging technologies such as voxel-based morphometry,[33] magnetization-transfer imaging,[25] and diffusion tensor MR imaging[34] are expected for further investigating the relative contributions of brain sub-structures for mapping and characterizing the neural networks of autism.

GENETIC PROFILE OF AUTISM IS CONTRIBUTED BY COMPLEX GENE VARIATIONS

Autism is currently recognized as a genetic disease, most likely resulted from multiplex genetics factors with or without the influence of before or after birth environments.[3]6 It is recognized that autism is one of the highest heritable disorders among psychiatric disease. Around 80% of monozygotic twins suffer from the same disease if acquired, compared to only 10% of sharing in dizygotic twins.[37,38] It affects predominately males with a male-to-female ratio of approximately 4.3:1, which might indicate an association with sex chromosomes.[39]

The genetic architecture of autism is not yet known. Autism is very likely a genetic disorder that results from simultaneous genetic variations related to multiple genes. Studies showed that although certain form of ASD may be transmitted in a Mendelian fashion within a single individual or family, for autism itself, common genetic variations in the population may contribute in a far more common and complex manner than Mendelian.[40,41,42] Large-scale genetic studies have been conducted in the last decade and shown clearly that the disease is not simply a Mendelian disorder.[43]

Despite various gene candidates have been proposed, none has been assigned to autism as disease-causing gene. Rare mutations have been identified in several synaptic genes, including neuroligin (NLGN3 and NLGN4X),[44] neurexin (NRXN1),[45] contactin (CNTN4) [46,47] and SH3 and multiple ankyrin repeat domain 3 (SHANK3).[42] Other candidate genes have been thought to be promising: GABA receptor, serotonin transporter genes, engrailed 2, MeCP2, Wnt2, and BDNF. Some of the genes encode neuronal cell-adhesion molecules that may be related to autism pathology. Some candidate genes have functions in synapse organization and are regulated by the trans-synaptic cell adhesion complex comprising the neurexins and neuroligins, both of which have been implicated in autism.[48] Genetic analysis has also observed a low functioning system featured with melatonin deficiency in a small number of autism population. Children with autism have been observed to show pineal gland hypofunction, with low melatonin production and co-occurrence of sleep disturbances and altered circadian rhythms.[49] Mutations in splicing or promoter region in the ASMT gene were detected in autism.[50] ASMT encodes for the last enzyme in melatonin synthesis and the altered ASMT gene can cause low expression or function of ASMT resulting in decreased level of melatonin.[49] Multiple small studies have demonstrated that 2 to 10 mg of melatonin may benefit autism patients with improved sleep.[52,52,53] Future study will need to identify melatonin's long term therapeutic effect on autism for the improvement of communication and language deficiency.

Copy number variations (CNVs) (in contrast to amino acid coding region mutations in single genes) are indications of genomic alteration in a general fashion rather than restricted. CNVs were found enriched in ASD cases compared to controls. CNVs of both deletion and duplication were recurrently observed in 5-10% of ASD cases in several chromosomes. Genomic regions with heritable CNVs may carry substantial risk for ASD including autism as reported recently in several studies.[54,55] Some CNV studies have revealed clustering of genes in multiple signaling pathways in autism. For example, CNVs within or surrounding genes related to ubiquitin pathways, were found in autism.[56] The affected genes include UBE3A, PARK2, RFWD2 and FBXO40. Since these targeted genes are involved in neuronal cell-adhesion or ubiquitin degradation, both important gene networks may contribute to the susceptibility of ASD. Furthermore, the consequence of genetic modifications on the gene products might have restructured those important pathways and ultimately the delicate function of the brain.

Overall, genetic alterations are multiplexed and in a complicated fashion in autism. Pathway involvement rather than single gene change has been found in independent autism research centers worldwide. This might have served as a biological basis for the etiology and pathophysiology of autism discussed in later paragraphs.

PHYSICAL CONDITIONS OF AUTISM ARE GENERALLY ASSOCIATED WITH ANXIETY AND OXIDATIVE STRESS

Numerous studies have been conducted to unravel the etiology of autism but the precise cause of autism remains largely elusive. Up to date, autism can be only considered a multi-factorial disorder that may involve biological factors from genetics as well as additional environmental contributors. Recently, systemic studies have been demonstrating that autism patients may have increased vulnerability to oxidative stress which may link genetics and environment together for integrative consideration.[57]

Oxidative stress is an emergent or chronic condition caused by the imbalance between the production of active free radicals (reactive oxygen species or ROS) and the repair of ROS-caused damage.[58] Although it is essential for human body to maintain certain level of ROS production for immune protection[60] and cell signaling,[59] excessive normal oxidative state is harmful to tissues and can cause toxic effects through the reaction of the free radicals with cellular components. Because of the non-specific biochemical redox reaction, ROS is able to damage any component of the cell, including proteins, lipids, DNA and numerous other small molecules.[61] Oxidative stress is involved in many human diseases, especially neuro-psychological diseases (or related conditions) including schizophrenia, bipolar disorder, fragile X syndrome, chronic fatigue syndrome, Alzheimer's disease, Parkinson's disease, and myocardial and heart disease.[57]

It is known that children have low level of glutathione from conception through infancy.[62,63] Due to the lack of glutathione-producing capacity by neurons, the brain has a limited capacity to detoxify ROS. Antioxidants such as glutathione are required for neuronal survival during the early critical period,[64] however as a metabolically active organ, the child brain is vulnerable to oxidative stress due to its limited antioxidant capacity, higher energy requirement, and higher amounts of lipids and iron which usually serves as redox catalytic agent.[65] The brain makes up about 2% of body mass but consumes 20% of total oxygen and the vast majority of oxygen consumption is used by the neurons.[13] Neurons apparently are the most susceptible to oxidative stress damaging when excessive ROS is generated, especially in children.

As indicated by recently conducted genetic studies, autism patients may have altered neuronal adhesion proteins and ubiquitin pathways that might have been modified by genomic regions associated with NLGN1, ASTN2, UBE3A, PARK2, RFWD2 and FBXO40 genes. The related pathways are associated with cellular stress and ROS production in pathological conditions.[67,68,69] Evidence began to accumulate that oxidative stress influence autism disease status since oxidative stress markers and abnormal DNA methylation have been found in patient's samples. Oxidative protein/DNA damage and DNA hypomethylation (epigenetic alteration) have been found in patients.[70] The oxidative stress related metabolic profile of unaffected siblings differed significantly from affected case siblings but not from normal controls. These data indicate autism has deficit in antioxidant and methylation capacity, which might lead to cellular damage and altered epigenetic gene expression.

It is implicated that there might be a shared mechanism from the role of oxidative stress in the pathogenesis of neuropsychiatric diseases including autism.[71,72] Oxidative stress may play a role as a mechanism linking the risk factors and pathological pathways described above. Results from clinical trials with antioxidant N-Acetyl Cysteine (NAC) are anticipated to give important clues and links to the hypothesis in the near future.[73]

In fact, it is commonly recognized that autism and anxiety go hand-in-hand.[74] Anxiety as well as depression is always accompanying people with autism (and their relatives).[75] These issues have been additional burdens for individuals to bear and are impacting heavily on their daily functioning.[76] Autism affects patients' ability to communicate with others and understand the surrounding world. This is often bound to cause anxiety or panic situations. Anxiety overload becomes even more burdened when changes in daily life happen to alter child's routine and subsequently increase anxiety and aggressive behaviors.[77] For anxiety condition that affects child and family's life seriously, many parents choose to use anti-anxiety drugs for their autistic children (see Table above). These treatments may reduce autism children's aggression behavior but often cause sedation and neuromuscular dysfunction.[78] Epidemiological surveys have revealed that between 15% and 30% of people with autism also suffer from certain degree of epilepsy [79] and need treatment (see Table above). Autism neurons might undergo high activity causing often, long and constant firing during early neurogenesis developmental window which then causes permanent damage and even epilepsy.[80] 40% of people with autism also have electrical discharges on EEG recordings, as opposed to just 2% in a normal population, also suggesting an oversaturated brain activity.[81]

Anxiety and oxidative stress may also happen one after another or simultaneously in autism brain.[82] Animal modeling study reveals the presence of oxidative stress in the central and peripheral systems linked to anxiety. These findings suggest the redox system in anxious condition may play a role in brain damage.[83,84] Interestingly, a study carried out in University of Granada's Institute of Biotechnology shows that melatonin administration to mice could neutralize oxidative damage and delays the neurodegenerative process of aging. Researchers believe this mechanism of action might contributed to melatonin's therapeutic effect in human autism considering that melatonin itself is also a powerful antioxidant that is able to penetrate and work in brain.[49] Melatonin administration in ASD was associated with improved sleep parameters, better daytime behavior, and minimal side effects. This might have been achieved by its potent antioxidant role described previously in addition to the improvement of sleep and reduced anxiety level in autism. Another example of anti-oxidant therapy is from a recent completed clinical trial of treatment of autism with

minocycline conducted by the NIH, National Institute of Mental Health (NIMH). The mechanism of minocycline delays neurodegeneration is based upon the anti-inflamation, antioxidative stress and apoptosis preventing effects of the drug. It would be very interesting to learn the trial results in the near future.[85,86]

NEUROPLASTICITY AS THERAPEUTIC BASIS IS HIGHLY INDICATED BY THE DISEASE FEATURES OF AUTISM

The most distinctive feature of human brain is that it is a highly adaptive system, especially cerebral cortex.[87] human brain is able to perform self-changing function under proper external support. In normal condition, human mental capacity is able to process broadly varied information and complex new experiences. The brain's ability to rebuilt itself and to act and react in ever-changing environment is known as multiple term including neuroplasticity, brain plasticity, neural plasticity, or central nervous system plasticity,[88,89,90] which at the electron microscopic level, is achieved at the inter-neuron level by the synaptic plasticity.[91] Normally, at birth, neuroplasticity (synaptic plasticity) allows the estimated 80-100 billion neurons to continually form brain-wide neural network for the inter-neuronal communication with 10,000 synapses from each neurons. Neuroplasticity is best demonstrated in the process of brain development in the first two years of life. Neuron numbers decline when entering into adulthood and the ineffective or rarely used connections are eliminated with certain well used synapses remaining in brain.[93,94] Recent studies on adult brain also demonstrated that human neural connections do not ever reach a fixed pattern but rather they can undergo remodeling in certain areas of brain.[95] For example, study from primates suggest that even a few months training with specific targeting of functional lobules of brain could change the structure of brain map. Under the stimulation, the corresponding brain area grew significantly with enlarged size. This probably achieved by generating new synapses from existing neurons or regenerating entirely from neural stem cells into new neurons.[ii] While this neural regeneration was long believed to be impossible after age 3 or 4, research now shows that new neurons can develop late into the life span, even into late stage of approximately year 60.[97] These findings suggest human brain possess adaptive flexibility, regenerative capacity, and remarkable efficiency throughout life. Neuroplasticity holds the key to the development of many new and more effective treatments for brain damage or degenerative diseases.[98,99] Neuroplasticity also offers hope to people suffering from cognitive disabilities or disease including autism. The potential of the brain's plasticity is expected to take advantage of basic research advancement in human biology.

It is now widely hypothesized that a disturbed neural network including the temporo-parietal cortex, limbic system, cerebellum, prefrontal cortex, and corpus callosum is involved in pathophysiology of autism. Considering the broad pathological involvement, it is not surprising that autism might not have mutated single protein but rather have an imbalanced brain of retarded total efficiency (with less common cases of Asperger Syndrome which might turn the imbalanced system into a beneficial aspect on certain functions such as remembering rote and rigid structures while lack of certain brain functions.[100] The hypothesized imbalance could have been the result of undesired change of multiple biological pathways. This is particularly important because most of the structures have been established in the early life of patients and it's with hope that early alteration would be largely beneficial to autism children. It would be the key to efficiently deal with this imbalance at very early childhood. As discussed in previous context, so far the time of autism diagnosis has been at the end stage of neurogenesis in childhood. Study on adult neuroplasticity has provide sound evidence that late stage of childhood brain is able to undergo remodeling with potential and power of neuroplasticity even if they have passed the previously described the "critical" developing stage. Progress in the field of neuroplasticity and its ultimate application in clinical medicine or social training would hold enormous potential contributing to autism therapy.[101]

Two drugs, haloperidol as well as arguably olanzapine, have been shown in psychological disorders to effect in modifying whole brain grey matters. This longitudinal, tightly controlled study followed patients up for nearly 100 weeks with magnetic resonance imaging (MRI) assessments and neurocognitive outcome evaluation in 14 academic medical centers (United States, 11; Canada, 1; Netherlands, 1; England, 1). a conventional antipsychotic, haloperidol (2-20 mg/d), or an atypical antipsychotic, olanzapine (5-20 mg/d). The author concluded that the differential treatment effects on brain morphology could be due to haloperidol-associated toxicity or greater therapeutic effects of olanzapine. However this conclusion has been chllenged from another angle which hypothesizes that olanzapine might also involve neuroplasticity for autism.[102,103]

CONCLUDING REMARKS

It is believed that autism patients undergo synaptic connection deficiency in early life, which might be associated with anxiety, stress, and the damaging effect of excessive ROS production. It would be important to track the status of ROS system in autism patient body and keep this dangerous system in balance during neurogenesis and brain functioning. Combining genetic profiling, biological pathway analysis, and brain mapping with neuroimaging technologies, neuroplasticity may hold the key for autism therapy for the regeneration of functional synapses. Based upon systemic neuroimaging and brain mapping with novel technologies towards localized and specified brain training, we may be able to optimize the autism pathological brain structure and neuronal network towards social and communication benefits. It can also be anticipated to combine small molecule drug treatment on autism to aid the neural regeneration efforts.

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